Prospective Study of Microalbuminuria as Predictor of Mortality in NIDDM

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Retrospective studies of patients with non-insulin-dependent diabetes mellitus (NIDDM) have suggested that microalbuminuria predicts early all-cause (mainly cardiovascular) mortality independently of arterial blood pressure. These findings have not been confirmed in prospective studies, and it is not known whether the predictive power of microalbuminuria is independent of other major cardiovascular risk factors. During 1985–1987, we examined a representative group of 141 nonproteinuric patients with NIDDM for the prevalence of coronary heart disease and several of its established and putative risk factors, including raised urinary albumin excretion (UAE) rate. Thirty-six patients had microalbuminuria (UAE 20–200 μg/min), and 105 had normal UAE (<20 μg/min). At follow-up, an average of 3.4 yr later, 14 patients had died. There was a highly significant excess mortality (chiefly from cardiovascular disease) among those with microalbuminuria (28%) compared to those without microalbuminuria (4%, $P < 0.001$). In univariate survival analysis, significant predictors of all-cause mortality included microalbuminuria ($P < 0.001$), hypercholesterolemia ($P < 0.01$), hypertriglyceridemia ($P < 0.05$), and preexisting coronary heart disease ($P < 0.05$). The predictive power of microalbuminuria persisted after adjustment for the effects of other major risk factors ($P < 0.05$). We conclude that microalbuminuria is a significant risk marker for mortality in NIDDM, independent of the other risk factors examined. Its presence can be regarded as an index of increased cardiovascular vulnerability and a signal for vigorous efforts at correction of known risk factors. *Diabetes* 41:736–41, 1992

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Received for publication 12 June 1991 and accepted in revised form 2 January 1992.

Clinical diabetic nephropathy, classically heralded by the appearance of persistent proteinuria, is a major complication of diabetes mellitus affecting up to 35% of patients with insulin-dependent diabetes mellitus (IDDM) (1) and is associated with a greatly increased risk of renal failure and death (2). A substantial proportion of this excess mortality is due to coronary heart disease (CHD; 2,3). A subclinical increase in urinary albumin excretion (UAE; microalbuminuria) early in the course of IDDM is a powerful predictor of the later development of persistent proteinuria and renal failure (4). Proteinuria is also a feature among patients with non-insulin-dependent diabetes mellitus (NIDDM), but renal failure is a much less common consequence, at least in white subjects, than in IDDM (5). The major cause of the excess morbidity and mortality among white NIDDM is cardiovascular disease (CVD) (6).

Three retrospective studies have suggested that microalbuminuria predicts all-cause (largely cardiovascular) mortality in NIDDM patients independently of arterial blood pressure, age, duration of diabetes, and level of glycemia (7–9). These findings have not been confirmed by prospective studies, and it is not known whether the predictive ability of microalbuminuria is independent of other major cardiovascular risk factors, e.g., hypercholesterolemia and smoking, which are associated with albuminuria (10,11). We report on the predictive power of microalbuminuria for mortality in a prospective study of a cohort of NIDDM patients in which other major risk factors measured at baseline, including smoking, arterial blood pressure, and serum lipids and lipoproteins, were taken into account.

RESEARCH DESIGN AND METHODS

The cohort for this prospective study was assembled from white NIDDM outpatients 31–64 yr old who attended the Lewisham Hospital diabetes survey from 1985 to

1987. The procedures and methods used in the baseline cross-sectional study have been described previously (12). In brief, NIDDM was defined by diagnosis after the age of 30 yr, without the use of insulin in the 1st yr after diagnosis and without history of ketosis. Diagnosis was based on a random venous plasma glucose level >11.1 mM confirmed by a second raised value (≥7.8 mM fasting or 11.1 mM random; 13).

Examination of the medical records of 1010 patients attending Lewisham Hospital Diabetes Clinic in 1984 (patients whose hospital number appeared at least once on the weekly clinic lists for 1984) revealed 646 NIDDM patients. Three-hundred fourteen of these patients in the 31–64 yr age-range were invited to a morning screening clinic during 1985–1987. Patients were asked to attend after a 12- to 14-h overnight fast, bringing a timed overnight urine collection for measurement of urinary albumin excretion rate (UAE), and 276 (88%) responded. Patients were systematically screened for selected indices of CVD and several of its risk factors. Eighty-seven (32%) were of Afro-Caribbean ethnic origin, 20 (7%) were Indian Asians, and 169 (61%) were of European (white), mostly British, ethnic origin. Because ethnic origin may affect susceptibility to diabetic complications, this analysis was confined to white patients.

For collection of the urine sample, a 2-L plastic container (containing 0.5 ml 1% wt/vol sodium merthiolate as preservative) was sent to each patient a few days before their clinic visit. Clear instructions on how to collect a timed overnight urine sample were also sent, and patients were asked to bring the whole sample to the clinic with them. The timing and performance of the collection was checked with each patient, and urine volume was measured to the nearest 2 ml. Of the 169 white patients, 164 (97%) submitted a timed overnight urine sample. Urine was cultured in samples positive for protein, blood, or nitrite on dipstick testing (N-Labstix, Ames, Miles, Bucks, UK). Exclusions were made on the basis of hematuria (3 men, 4 women), evidence of urinary tract infection (10 women), or clinical proteinuria (4 men) defined by AER ≥ 200 μg/min. Two other men were excluded because of renal carcinoma. No patient had clinical evidence of congestive heart failure.

Of the remaining 141 patients forming the cohort, 69% were taking oral antidiabetic therapy, 4% were on injected insulin, and 27% were treated by dietary advice alone. The only patient being treated with plasma lipid–lowering agents was excluded on the basis of clinical proteinuria.

Fasting venous blood samples were collected, weight and height were measured in indoor clothing without shoes, and body mass index (BMI; wt[kg]/ht[m^2]) was calculated. Information on past medical history, smoking habits, alcohol consumption, and cardiovascular symptoms was collected with standard questionnaires. Arterial blood pressure (diastolic 5th phase) was recorded as the mean of two measurements made in the sitting position and in the right arm with a standard clinical sphygmomanometer (cuff size 14 × 42 cm) by the same observer after at least 10 min of rest. A resting 12-lead electrocardiogram (ECG) was recorded and analyzed according to the Minnesota code (14).

Urinary albumin concentration was estimated by radioimmunoassay (15) (between batch coefficient of variation 8%) albumin excretion rate (AER μg/min) was calculated as the product of urine flow (ml/min) and albumin concentration (μg/ml). The major serum lipoprotein classes, very-low-density lipoprotein (VLDL), LDL, and high DL (HDL), were separated by preparative ultracentrifugation (16). The HDL_2 and HDL_3 subclasses were separated by ultracentrifugation from the supernatant remaining after removing VLDL and LDL from serum by chemical precipitation with dextran sulphate and magnesium chloride. Serum total and lipoprotein fractional triglycerides and cholesterol were assayed by enzymatic methods (Boehringer Mannheim, East Sussex, UK) with a Cobas-Bio centrifugal analyzer (Roche, Herts, UK). HBA_1 was assayed by electroendosmosis after removal of the unstable adduct (Ciba-Corning, Essex, UK; laboratory reference range 4.9–7.5%). Serum insulin was assayed by a double-antibody radioimmunoassay (Pharmacia, Uppsala, Sweden). Plasma creatinine was assayed by a kinetic Jaffe method and plasma glucose by a hexokinase method (Roche).

Smokers and exsmokers were defined as those currently smoking or having smoked one or more cigarettes per day for ≥1 yr. Alcohol consumption was defined by the number of drink units consumed per week (a drink unit is 285 ml beer or lager, 115 ml wine or 25 ml liquor). Hypertension was defined as a systolic blood pressure of ≥160 mmHg and/or a diastolic blood pressure of ≥95 mmHg and/or a history of antihypertensive therapy. Hypercholesterolemia was defined as a serum cholesterol ≥6.5 mM and hypertriglyceridemia as a serum triglyceride concn ≥2.3 mM. CHD was considered present either by positive responses to the World Health Organization questionnaire (angina and/or previous myocardial infarction) or by ECG Minnesota codes 1–3: 4–1, 4–2, or 4–3 if accompanied by 5–1, 5–2, or 5–3 (possible ischemia) or 1–1, 1–2, or 7–1 (probable ischemia). All other codes and normal ECG were classified as no ischemia. The study was approved by the Lewisham Hospital ethics committee.

As part of an assessment of the prevalence of hyperlipidemia in NIDDM, patients who attended the original Lewisham survey, including the surviving members of our cohort, were reinvited to the screening clinic during 1988–1989. This analysis relates to mortality and its causes up to 1 October 1989 (mean follow-up period 3.4 yr; range, 2.4–4.3 yr). Death certificates for the 14 nonsurvivors were obtained from the Office of Population Censuses and Surveys, and the underlying cause of death was obtained from these. Additional information was available from postmortem reports (carried out in 8 patients) and from Hospital clinical records. With the exception of 1 patient, life/death status was securely established for all members of the cohort; a search for death registration of the single exception was negative.

Statistical analysis was carried out with SAS and BMDP packages (17,18). AER, serum total, VLDL triglycerides, and VLDL cholesterol were log transformed because of

TABLE 1
Associations with microalbuminuria in non-insulin-dependent diabetic men and women

	Men		Women	
	Microalbuminuria	Normoalbuminuria	Microalbuminuria	Normoalbuminuria
n	27	55	9	50
Age (yr)	55.9 (1.7)	55.5 (1.0)	58.6 (2.1)	56.8 (1.1)
Diabetes duration (yr)	6.5 (0.7)	5.2 (0.6)	7.3 (1.8)	5.0 (0.5)
HbA_1 (%)	9.7 (0.4)*	8.5 (0.2)	10.6 (0.7)*	9.0 (0.3)
Body mass index (kg/m^2)	30.5 (0.9)†	27.7 (0.6)	32.0 (1.6)	29.9 (0.7)
Serum insulin (pM)	90.0 (11.4)*	62.4 (5.4)	80.4 (12.0)	78.6 (6.0)
Systolic blood pressure (mmHg)	147 (3)	139 (3)	145 (6)	146 (3)
Diastolic blood pressure (mmHg)	88 (2)*	81 (1)	82 (3)	81 (2)
Hypertension				
n	19*	17	5	25
%	70*	31	56	50
Triglycerides (mM)‡	2.66*	1.92	2.80*	1.85
95% Confidence intervals	2.33–3.04	1.77–2.09	1.62–4.38	1.57–2.14
Cholesterol (mM)	6.45 (0.27)*	5.78 (0.16)	7.84 (0.64)*	6.28 (0.18)
Low-density lipoprotein cholesterol (mM)	4.06 (0.23)*	3.50 (0.13)	4.89 (0.44)*	3.88 (0.15)
Coronary heart disease				
n	13*	14	8†	13
%	48.2*	25.5	89†	26

Values are means (SE).
*$P < 0.05$, †$P < 0.01$ (within-sex comparisons).
‡Geometric mean.

their positively skewed frequency distributions. Differences in mean values were tested with an unpaired *t* test; consistent conclusions were reached with the nonparametric Kruskal-Wallis test. Proportions were compared with Fisher's exact χ^2 test. All tests were two-sided. When considering all-cause mortality, the Cox proportional hazards model was used (19). The Cox model was used in preference to the logistic model because of the relatively large variation in follow-up time.

Univariate results (age-adjusted) were calculated for continuous and class variables; where class variables were used, the relative risks (hazards) were estimated. The stepwise Cox analysis considered all those variables significant at the univariate level; significance levels for entry to, and exit from, the model were set equal to 10%.

RESULTS

The prevalence of microalbuminuria in men significantly exceeded that in women (32.9 vs. 15.3%, respectively; $P < 0.05$). Clinical and biochemical features of men and women with and without microalbuminuria are compared in Table 1. The presence of microalbuminuria was not associated with significant differences in mean age and known duration of diabetes in these groups. In men but not women, microalbuminuria was associated with significantly increased BMI and serum insulin concentration. Microalbuminuric patients had higher proportions of HBA_1 in both sexes and this was accompanied by significantly raised fasting plasma glucose concentration in microalbuminuric women (mean ± SE 12.4 ± 1.0 vs. 9.6 ± 0.4 mM; $P < 0.05$) but not men. Men with microalbuminuria had a significantly higher diastolic blood pressure and an increased prevalence of hypertension, but the difference in systolic pressure was more likely to have arisen by chance ($P = 0.07$). Microalbuminuric women showed no significant difference in systolic or diastolic blood pressure or in the prevalence of hypertension. Overall, 36% of patients (35% men, 39% women) were being treated with antihypertensive medications, whereas 11% were hypertensive (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg) but were untreated at the time of screening. Among microalbuminuric patients, there was an increased frequency of antihypertensive medication use compared to that in normoalbuminuric subjects (men 56% [15 of 27] vs. 24% [13 of 55], $P < 0.01$; women 67% [6 of 9] vs. 34% [17 of 50], $P = 0.13$). However, there was no significant difference between mean AER of patients on antihypertensive medication compared with that of patients who were hypertensive but not on treatment ($P = 0.25$).

In both men and women, microalbuminuria was associated with significantly increased fasting serum triglycerides and total and LDL cholesterol. Microalbuminuric men, but not women, also had significantly increased concentrations of VLDL triglycerides (geometric mean 1.92, 95% confidence interval [CI] 1.43–2.27 mM vs. 1.22, 0.95–1.51 mM, $P < 0.05$) and VLDL cholesterol (0.80, 0.59–1.09 mM vs. 0.51, 0.40–0.66 mM, $P < 0.05$). In men and women, microalbuminuria was associated with a significantly increased prevalence of CHD. Microalbuminuria was not significantly associated with differences in the proportions of current or exsmokers and patients on different antidiabetic treatment modalities or in mean alcohol consumption, plasma creatinine, and the cholesterol concentrations of HDL and its subfractions.

Mortality at follow-up. During the mean 3.4-yr follow-up period to October 1989, 14 (8 men, 6 women) of 141 (10%) patients had died. The underlying causes of death are shown for each patient in Table 2 together with sex and baseline AER. Ten of 36 (28%) patients with microalbuminuria had died compared with 4 of 105 (4%) patients

TABLE 2
Cause-specific mortality among non-insulin-dependent diabetic patients

Patient	Sex	Albumin excretion rate (μg/min)	Underlying cause of death
1	F	2.7	Carcinoma of the pancreas
2	F	3.3	Renal cell carcinoma
3	M	6.6	Carcinoma of the colon
4	M	7.1	Alcoholic liver disease
5	M	21.4	Myocardial infarction
6	F	26.0	Stroke
7	F	34.0	Coronary thrombosis
8	M	35.3	Myocardial infarction
9	M	36.6	Carcinoma of the stomach
10	F	72.8	Myocardial infarction
11	M	93.5	Myocardial infarction
12	F	98.5	Chronic emphysema
13	M	130.0	Myocardial infarction
14	M	155.0	Ischemic heart disease

with normoalbuminuria ($P < 0.001$). Eight of 10 microalbuminuric patients had died from CVD; 7 from ischemic heart disease (ICD codes 410–414); 1 from stroke. No death in the normoalbuminuric cohort was registered as due to CVD. Renal disease was not recorded as either an underlying or contributory cause of death in any of these 14 patients. Diabetes mellitus was mentioned as a contributory cause of death on only 3 of 14 death certificates.

Cox survival analysis—adjusting for age only. Possible predictors of all-cause mortality were examined in age-adjusted Cox survival analysis. The continuous variables tested included log AER, log serum total and VLDL triglycerides; total and LDL cholesterol; HDL, HDL_2, and HDL_3 cholesterol; systolic and diastolic blood pressures; alcohol consumption; duration of diabetes; serum insulin; HBA_1 and plasma glucose; and creatinine. Of these, only log AER ($P = 0.0035$), log total triglycerides ($P = 0.0313$), total cholesterol ($P < 0.0001$), and LDL cholesterol ($P < 0.0001$) were significantly associated with mortality. Sex adjustment did not significantly affect these findings. The following categorical variables were also examined: microalbuminuria, sex, hypertension, current smoking, CHD, antihypertensive treatment, hypercholesterolemia, and hypertriglyceridemia. Only microalbuminuria, hypercholesterolemia, hypertriglyceridemia, and CHD were significantly associated with all-cause mortality (Table 3).

Multiple regression. When microalbuminuria was entered into an age-adjusted Cox model with the established major risk factors, hypertension, smoking, and hypercholesterolemia, only microalbuminuria and hypercholesterolemia emerged as significant predictors of mortality (relative risks and 95% CIs were 5.1, 1.5–17.3; and 5.3, 1.1–25.3, respectively). When categorical variables showing a significant univariate association with all-cause mortality were entered into an age-adjusted Cox model (Table 4), microalbuminuria emerged as the only significant predictor of mortality ($P < 0.05$). In an age-adjusted stepwise analysis, which considered all continuous and categorical variables significant at the univariate level, the final model contained serum cholesterol ($P < 0.001$) and microalbuminuria ($P < 0.05$).

TABLE 3
Cox univariate analysis for all-cause mortality

	Relative risk	95% Confidence interval
Coronary heart disease	3.32*	1.10–10.00
Hypertriglyceridemia	3.32*	1.08–10.30
Hypercholesterolemia	8.10†	1.79–36.70
Microalbuminuria	7.92‡	2.50–25.30
Sex (M/F)	1.12	0.39–3.23
Hypertension	1.66	0.55–5.00
Current smoking (yes/no)	1.85	0.65–5.29
Antihypertensive treatment	2.03	0.70–5.86

Results are age-adjusted.
*$P < 0.05$.
†$P < 0.01$.
‡$P < 0.001$.

DISCUSSION

This prospective study, based on a cohort of white NIDDM out-patients recruited from 1985 to 1987, shows that microalbuminuria is an independent predictor of all-cause, chiefly cardiovascular, mortality, supporting our previous cross-sectional findings of an association between AER and CHD morbidity in these patients (12). In an earlier study, Jarrett et al. (7) found that AER, measured from a single overnight urine collection, as in this study, was strongly predictive of all-cause (mainly cardiovascular) mortality in a retrospective review of 44 NIDDM patients. In that study, the predictive power of AER was independent of age, sex, diabetes duration, and arterial blood pressure; cutoff points of 10 or 30 μg/min, used to define the lower limit of microalbuminuria, had similar discriminative ability of mortality prediction. Similarly, Mogensen (8), in a 9.5-yr retrospective study of 232 NIDDM patients, reported that increases of urinary albumin concn >15 μg/ml were predictive of declining survival, independently of age, sex, plasma glucose, and blood pressure; albumin concn between 30 and 140 μg/ml also predicted the development of clinical proteinuria as in IDDM patients (4). An extension of this study to 503 NIDDM patients (9) confirmed these earlier data and showed that the major cause of death was CVD.

However, these three survival studies were retrospective in design and thus were potentially subject to more sources of error than prospective studies (20). In each case, the study outcome variable was used to derive the

TABLE 4
Multiple regression analysis for mortality

	Relative risk	95% Confidence interval
Coronary heart disease	1.52	0.45–5.18
Hypertriglyceridemia	1.36	0.40–4.65
Hypercholesterolemia	4.74	0.94–23.90
Microalbuminuria	4.08*	1.09–15.19

Results are age-adjusted.
*$P < 0.05$.

level of AER or concentration associated with increased mortality risk. Furthermore, the predictive power of microalbuminuria was not demonstrated to be independent of either hypercholesterolemia or smoking, which are known to be important CVD risk factors in diabetes (21). Several studies have reported cross-sectional associations between plasma lipids and lipoproteins and albuminuria in IDDM (11,22) and NIDDM (12,23,24) and also between smoking and albuminuria in IDDM (10) and NIDDM (25). These factors could confound an apparent link between microalbuminuria and morbidity and mortality outcomes. In this study, microalbuminuria was defined as an AER between 20 and 200 μg/min, as recommended (albeit for IDDM) by a consensus conference (26).

At baseline, we found a 25% prevalence of microalbuminuria, with a higher prevalence in men than women. This is comparable to the 27% prevalence reported in a recent Danish hospital-based study of NIDDM patients (27). Despite a high response rate in our initial examination, referral bias cannot be excluded (28). The cause of referral was most unlikely to have been microalbuminuria because sensitive measurements of urinary albumin concentration were not available to most referring physicians at the time. However, a higher prevalence of diabetic complications would be expected in a hospital-based than in a population-based study. In community-based studies of NIDDM, Gatling et al. (29) found only an 8% prevalence of microalbuminuria defined by AER ≥30 μg/min (our prevalence with this definition was 18%); however, bias was likely because only 54% of the population responded. In contrast, Damsgaard and Mogensen (30) reported a high prevalence of microalbuminuria (43% in men, 13% in women) in a population study of elderly hyperglycemic subjects with no history of diabetes; the prevalence was still higher in known diabetic subjects. Microalbuminuria may be a less specific finding in NIDDM than IDDM because <70% of clinically proteinuric NIDDM patients show histological evidence of diabetic nephropathy (31).

Plasma lipid and lipoprotein concentrations are associated with microalbuminuria in NIDDM (12,23,24), and Niskanen et al. (23), in a 5-yr prospective study of newly diagnosed NIDDM patients, demonstrated that microalbuminuria may precede the development of lipoprotein disturbances. The independent association of raised AER with CHD that we described (12) was also noted by Gatling et al. (25), with albumin:creatinine ratios in random urines; it also may be present at the diagnosis of NIDDM (32). The observed association of both serum insulin concentration and CHD with microalbuminuria in men in this study raises the possibility that insulin resistance may be a common factor; however, further studies are needed to investigate this question. AER is also related to peripheral vascular disease in NIDDM (32,33). Of interest, these associations have been described even in nondiabetic subjects (34) and microalbuminuria predicted early mortality in a 3.6-yr follow-up.

At follow-up, we found a substantial excess mortality among NIDDM patients with microalbuminuria compared to those with normal AER. This difference was largely due to cardiovascular deaths, but the relatively small number of fatal events justifies only cautious conclusions. The finding that renal disease was not an underlying cause of death in any patient in this NIDDM cohort agrees with previous observations showing renal disease mortality to be an uncommon outcome in white NIDDM patients (5,7–9). This is in contrast to the findings in nonwhite cohorts (35).

In univariate survival analysis, microalbuminuria and the continuous variable AER had a strong association with all-cause mortality; this was also the case for hypercholesterolemia and the continuous variables serum total and LDL cholesterol. Hypercholesterolemia has been previously found to be an important predictor of all-cause and cardiovascular mortality in diabetes mellitus (21) and in the general population. Hypertriglyceridemia and the continuous variable serum triglycerides was also significantly, but less strongly, associated with mortality. There is clearer evidence of triglycerides as a risk factor for CHD in diabetes than in the general population (36). Preexisting CHD morbidity was also significantly associated with all-cause mortality in univariate analysis.

Increased arterial blood pressure is also a major CVD risk factor in NIDDM (37). At baseline, we found a significant association between microalbuminuria and both diastolic blood pressure and the prevalence of hypertension in NIDDM men but not in women. However, neither systolic or diastolic blood pressure nor the categorical variable hypertension had a significant univariate association with subsequent mortality. This was also the case when other established or putative CVD risk factors were tested in Cox models. However, because of the small number of deaths, this study has limited power in identifying weaker risk factors. As a result, firm conclusions should not be reached on the basis of lack of statistical significance.

In an age-adjusted multiple regression containing all categorical variables significant at the univariate level, only microalbuminuria emerged as a significant predictor of mortality. In an age-adjusted stepwise analysis, which considered all continuous and categorical variables significant at the univariate level, serum cholesterol had the strongest association with mortality followed by microalbuminuria with no other variable being significant. These prospective findings support the earlier retrospective studies (7–9) and establish an effect independent of other CHD risk factors. Ideally, to analyze the true predictive power of microalbuminuria, we would have removed those with CHD at entrance. However, because 70% of those who died had baseline CHD, further analysis would have been impractical. We therefore examined the full group and adjusted for baseline CHD in our analysis.

The mechanism of the link between microalbuminuria and cardiovascular mortality is unknown. However, increased urinary albumin loss has been postulated to be a marker of a generalized increase in vascular permeability, which might predispose to greater penetration into the arterial wall of atherogenic lipoprotein particles (38). The practical implication of this study is that the risk factors for early mortality in NIDDM, microalbuminuria,

and hypercholesterolemia are readily detectable and are potentially modifiable. There is no direct evidence that reducing AER or serum cholesterol, which is possible by numerous therapeutic maneuvers (39,40), will affect cardiovascular morbidity and mortality in NIDDM, and there is a pressing need for more information from controlled trials.

In conclusion, the presence of microalbuminuria in NIDDM can be regarded as an index of increased cardiovascular vulnerability and a signal for vigorous efforts at correction of known risk factors.

ACKNOWLEDGMENTS

This study was supported in part by a British Diabetic Association Group Grant and by funding from Duncan, Flockhart and Co., Ltd.

We thank Graham Scott, Anne Dredge, Jonathan Maddern, and Andrea Collins for technical help. We are grateful to Nan Keen for Minnesota coding of ECG recordings and Dr. M.R. El-Gohari for clinical support in the original survey.

Parts of this study were reported in abstract form at the 26th meeting of the European Association for the Study of Diabetes, September 1990, Copenhagen.

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