Relationship Between Risk Factors and Mortality in Type 1 Diabetic Patients in Europe

The EURODIAB Prospective Complications Study (PCS)

SABITA S. SOEDAMAH-MUTHU, PHD[1,2]
NISH CHATURVEDI, MD[3]
DANIEL R. WITTE, PHD[2]
LYNDA K. STEVENS, MSC[2]
MASSIMO PORTA, MD[4]
JOHN H. FULLER, FRCP[2]
FOR THE EURODIAB PROSPECTIVE COMPLICATIONS STUDY GROUP

OBJECTIVE — The purpose of this study was to examine risk factors for mortality in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Baseline risk factors were measured in the EURODIAB Prospective Cohort Study with 2,787 type 1 diabetic patients (51% men and 49% women) recruited from 16 European countries. Mortality data were collected during a 7-year follow-up.

RESULTS — There was an annual mortality rate of 5 per 1,000 person-years in patients with type 1 diabetes (mean age at baseline 33 years, range 15–61 years); of the total 2,787 subjects, 102 died. The final multivariable model contained age at baseline (standardized hazard ratio 1.78 [95% CI 1.44–2.20]), A1C (1.18 [0.95–1.46]), waist-to-hip ratio (WHR) (1.32 [1.14–1.52]), pulse pressure (1.33 [1.13–1.58]), and non-HDL cholesterol (1.33 [1.12–1.60]) as risk factors for all-cause mortality. Macroalbuminuria (2.39 [1.19–4.78]) and peripheral (1.88 [1.06–3.35]) and autonomic neuropathy (2.40 [1.32–4.36]) were the most important risk markers for mortality. Similar risk factors were found for all-cause, non-cardiovascular disease (CVD), unknown-cause, and CVD mortality.

CONCLUSIONS — Important risk factors for the increased total and non-CVD mortality in type 1 diabetic patients are age, WHR, pulse pressure, and non-HDL cholesterol. Microvascular complications from macroalbuminuria and peripheral and autonomic neuropathy are strong risk markers for future mortality exceeding the effect of the traditional risk factors.

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The presence of type 1 diabetes is associated with a three- to fourfold increased risk of mortality compared with that of the general population (1,2). It is still not clear what risk factors explain this excess mortality risk. We have shown that risk factors associated with insulin resistance, such as triglyceride, waist-to-hip ratio (WHR), and albuminuria strongly predict cardiovascular disease (CVD) in type 1 diabetes (3). Although CVD is the major cause of death in patients with type 1 diabetes, it only accounts for approximately half of all deaths, and it is therefore important to study the totality of risk and non-CVD causes of mortality in this young population that is particularly vulnerable to premature death. Previous studies have often had too few deaths (4) or have not collected key risk factors at baseline (1,2). The few large cohort studies that have studied this question have produced inconsistent findings (4–6), in part because key common risk factors were not always included. Therefore, the aim of this study was to examine risk factors for all-cause mortality in a large, 7-year prospective cohort study of patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS

— Full details of the design, methods, and recruitment for the EURODIAB Prospective Complications Study (PCS) have been published elsewhere (7). This clinic-based prospective cohort study examined 3,250 type 1 diabetic patients between 1989 and 1991. Participants were aged between 15 and 60 years and were recruited from 31 centers in 16 European countries. The sampling frame was all type 1 diabetic patients attending each center at least once in the past year. Patients were stratified by age (three categories), diabetes duration (three categories), and sex. Ten patients were then randomly selected from each stratum (7). Type 1 diabetes was defined as diabetes diagnosed before the age of 36 years with a continuous need for insulin within 1 year of diagnosis. Of those invited, 85% participated. Those with duration of diabetes <1 year and pregnant women were excluded. Ethics committee approval was obtained at each center, and all subjects provided written informed consent.

Follow-up

Seven years after baseline examinations, study participants were invited for reexamination. Of the 3,250 subjects at baseline, 463 individuals could not be assessed; four centers ($n = 437$) did not participate in the follow-up examination. For the remaining 2,787 patients mortality data were collected during the follow-up (up to 1999). All events were captured by questionnaire, with additional supporting information from hospital records and death certificates. In addition, a comparison of allocation of

From the [1]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; [2]Epidemiology and Public Health, Royal Free and University College London Medical School, London, U.K.; the [3]National Heart and Lung Institute, Imperial College, London, U.K.; and [4]Medicine, University of Turin, Turin, Italy.
Corresponding author: S.S. Soedamah-Muthu, s.s.soedamah-muthu@umcutrecht.nl.
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cause of death was performed separately by two observers with 100% agreement.

Measurements

All risk factors and microvascular complications were measured at baseline according to a standardized protocol (8). Blood pressure was recorded in a sitting position with a random zero sphygmomanometer (Hawskley, Lancing, U.K.) and taken as the mean of two measurements. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg and/or the current use of blood pressure–lowering drugs (including ACE inhibitors, calcium channel antagonists, β-blockers, [thiazide] diuretics, and α-blockers). Pulse pressure was calculated as the difference between systolic and diastolic blood pressure.

Retinopathy was assessed by retinal photographs taken according to the EURODIAB protocol (9). Grading was performed by the Retinopathy Grading Centre at the Hammersmith Hospital, Imperial College London (London, U.K.). Retinopathy was classified as none (level 0), nonproliferative (levels 1–3), and proliferative (levels 4 and 5).

Distal neuropathy was diagnosed in patients with two or more of the following four measures (10): the presence of one or more symptoms, the absence of two or more reflexes of the ankle or knee tendons, a vibration perception threshold that was abnormal for the patient's age (11), and abnormal autonomic function (loss of heart rate variability with an RR ratio of <1.04 and/or postural hypotension with a fall in systolic blood pressure of ≥20 mmHg) (12). (For a definition of RR, see Tesfaye et al. [10]). "Pure" peripheral neuropathy was defined as distal neuropathy without autonomic symptoms or abnormal autonomic function test results. Autonomic neuropathy was defined in two ways: *1*) according to the above description (13) or 2) at least two abnormal tests with a RR ratio of <1.04 and postural hypotension with a fall in systolic blood pressure of ≥30 mmHg.

Laboratory measurements

A single 24-h urine collection was performed to calculate albumin excretion rate (AER) after excluding proteinuria due to urinary tract infection using a Nephur dip-stick test for bacteria. Urinary albumin was measured in a single laboratory by an immunoturbidimetric method (sanofi pasteur, Minneapolis, MN) (14). AER was categorized as normoalbuminuria (≤20 μg/min), microalbuminuria (between 20 and 200 μg/min), and macroalbuminuria (≥200 μg/min). Albuminuria was defined as micro- and macroalbuminuria. A blood sample was taken for the measurement of plasma lipids (fasting triglycerides, cholesterol, and HDL cholesterol) and A1C. Triglyceride (15) and cholesterol (16) concentrations of plasma and the cholesterol concentration of HDL (17) were assayed by standard enzymatic methods (Boehringer Mannheim, East Sussex, U.K.) using a COBAS BIO centrifugal analyzer (Roche, Welwyn Garden City, Herts, U.K.). For HDL cholesterol, samples with triglyceride concentrations >268 mg/dl were diluted with 0.15 mol/l sodium chloride solution before chemical precipitation. All analyses were performed centrally. LDL cholesterol was calculated from Friedewald's formula if triglycerides were <4 mmol/l (18). Non-HDL cholesterol was calculated as HDL cholesterol subtracted from total cholesterol. A1C was measured centrally by an enzyme immunoassay (Dako Ltd., Ely, U.K.) using a monoclonal antibody raised against A1C (19).

Statistical analysis

The statistical package Stata 7.0 (Stata Corporation, College Station, TX) was used to perform all analyses. $P < 0.05$ was considered statistically significant. Descriptive statistics were calculated. Spearman rank correlations were used to test the cross-sectional relationship between risk factors. Non-normally distributed variables were log-transformed. Mortality rates (per 1,000 person-years) were calculated. Univariate and multivariate Cox proportional hazards modeling was used to estimate hazard ratios (HRs) for mortality associated with risk factors. In analyses adjusted for age and duration of diabetes, mortality was split by non-CVD causes, CVD causes, unknown causes, and all causes. A simultaneous and stepwise approach was used to determine the most important risk factors. Risk factors were chosen from the unadjusted Cox models, selecting one of each entity of risk factors (e.g., either systolic or diastolic blood pressure or hypertension), using $P < 0.15$ as well as evidence from the literature. Microvascular complications (retinopathy, albuminuria, and peripheral neuropathy) were entered in multivariable models first alone and then in combination with risk factors.

Likelihood ratio tests were used to estimate the importance of each risk factor and to test interaction terms. A full model with a set of risk factors was compared with an incomplete model omitting the risk factor of interest from the previous model. The *P* value for the effect of removing a given risk factor from the model was obtained by comparing the log likelihoods from the two models. Standardized hazard ratios (sHRs) were estimated from these models by exponentiating the β-coefficient multiplied by the SD [exp(β × SD)].

Table 1—*Causes of death in patients with type 1 diabetes, EURODIAB PCS*

Cause of death	*n*
CHD	24
Other CVD	5
Cancer	9
Sudden death (non-CVD)	2
Respiratory	7
Traffic accident	5
Suicide/murder	5
Diabetes	4
Infection	5
AIDS	1
Unknown	35
Total	102

CHD was defined as myocardial infarction (8), cardiogenic shock (2), cardiac surgery (2), ischemic heart disease (7), heart attack (3), and sudden death (2). Other CVD was defined as cerebrovascular disease (1), cardiovascular (1), foot gangrene (1), pulmonary embolus (1), and heart failure (1). Non-CVD was defined as AIDS (1), suicide/murder (5), cancer (9), traffic accident (5), sudden death (2), diabetes (2), diabetes ketoacidosis (1), coma (1), respiratory (7), and infection (5).

RESULTS — Of the 2,787 (51% men and 49% women) type 1 diabetic patients (age at baseline 33 years, range 15–61 years), 102 (4%) died during 7 years of follow-up (64 men and 38 women; 21,760 person-years of follow-up). The causes of death were as follows (Table 1): causes from coronary heart disease (CHD) ($n = 24$, 24%), other CVD ($n = 5$, 5%), non-CVD ($n = 38$, 37%), and unknown causes ($n = 35$, 34%). The total annual mortality rate was 4.7 per 1,000 person-years [95% CI 3.9–5.7] with a mean age at death of 41 years. Mortality was greater in men than in women (5.8 per 1,000 person-years [4.5–7.4] vs. 3.6 per 1,000 person-years [2.6–4.9]; $P = 0.02$). The annual mortality rate for non-CVD causes was 1.9 per 1,000 person-years [1.4–2.6], for CVD causes was 1.4 per 1,000 person-years [1.01–2.08], and

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Table 2—*Baseline characteristics of the EURODIAB PCS cohort by life/death status*

	Died	Survived
n	102	2,685
Age at baseline (years)	41 ± 11	32 ± 10
Age at diabetes diagnosis (years)	20 ± 9	18 ± 8
Duration of diabetes (years)	22 ± 12	14 ± 9
A1C (%)*	8.8 ± 2.2	8.4 ± 1.9
Systolic blood pressure (mmHg)	135 ± 27	121 ± 17
Diastolic blood pressure (mmHg)	78 ± 15	75 ± 11
Pulse pressure (mmHg)	57 ± 21	45 ± 14
Cholesterol (mmol/l)	5.9 ± 1.3	5.3 ± 1.1
LDL cholesterol (mmol/l)	3.8 ± 1.1	3.3 ± 1.0
HDL cholesterol (mmol/l)	1.4 ± 0.5	1.5 ± 0.4
Fasting triglycerides (mmol/l)	1.1 (0.9–1.8)	0.9 (0.7–1.3)
Non-HDL cholesterol (mmol/l)	4.5 ± 1.4	3.8 ± 1.1
Waist-to-hip ratio (men/women)	0.93 ± 0.09/0.84 ± 0.13	0.88 ± 0.08/0.80 ± 0.11
BMI (kg/m^2) (men/women)	24.0 ± 2.9/23.5 ± 3.6	23.6 ± 2.6/23.5 ± 3.0
Insulin dose (units · day^{-1} · kg^{-1})	0.61 (0.49–0.75)	0.67 (0.54–0.81)
AER (μg/min)	54.1 (9.8–293.4)	10.8 (6.5–24.0)
Men	64 (63)	1,61 (51)
Current smoking	32 (31)	835 (31)
Low physical activity	55 (54)	1,197 (45)
2–3 insulin injections/day	92 (91)	2,510 (96)
Hypertension	56 (55)	595 (22)
Antihypertensive medication	36 (35)	225 (8)
ACE inhibitors	17 (17)	136 (5)
Calcium channel antagonists	12 (12)	44 (2)
β-Blockers	5 (5)	25 (1)
Diuretics	6 (6)	15 (1)
Thiazide diuretics	2 (2)	11 (0.4)
α-Blockers	0 (0)	8 (0.3)
Microalbuminuria	24 (26)	549 (21)
Macroalbuminuria	30 (31)	197 (8)
Albuminuria	54 (57)	746 (29)
Nonproliferative retinopathy	24 (38)	771 (35)
Proliferative retinopathy	22 (34)	210 (10)
Retinopathy	46 (72)	981 (45)
Autonomic neuropathy: *1*)†	59 (58)	818 (30)
Autonomic neuropathy: *2*)†	9 (9)	55 (2)
Peripheral neuropathy	58 (57)	569 (21)
Cardiovascular disease	28 (28)	211 (8)

Data are means ± SD, median (interquartile range), or *n* (%). *Corrected A1C values according to the Diabetes Control and Complications Trial method. †Autonomic neuropathy was defined in two ways: *1*) loss of heart rate variability with an RR ratio of <1.04 and/or postural hypotension with a fall in systolic blood pressure of ≥20 mmHg or *2*) loss of heart rate variability with an RR ratio of <1.04 and postural hypotension with a fall in systolic blood pressure of ≥30 mmHg.

for unknown causes was 1.7 [1.3–2.4] per 1,000 person-years.

Baseline risk factors were compared in those patients who were lost to follow-up ($n = 463$) with those included ($n = 2,787$). Distribution of risk factors was similar between these groups, except for a higher prevalence of smoking (38 vs. 31%), peripheral neuropathy (31 vs. 23%), and use of antihypertensive medication (15 vs. 9%) in those lost to follow-up compared with those remaining in the study (data not shown in tables).

Table 2 shows the baseline characteristics of the study population by overall mortality status. At baseline, those who subsequently died of any cause were older, had diabetes diagnosed at an older age, and had a longer duration of diabetes ($P < 0.0001$). Results for modifiable risk factors, including A1C, blood pressure, lipid profile, central obesity, and physical activity, were also worse at baseline. Total insulin dose and daily frequency of insulin injection were less in those who died, and the burden of other diabetes complications, both microvascular and macrovascular, was greater. Interestingly, BMI and smoking were not statistically significantly related to all-cause mortality, even in univariate analysis.

In Table 3 an overview is given of all risk factors and microvascular complications in relation to mortality in patients with type 1 diabetes. Mortality was split into non-CVD causes, CVD causes, and unknown causes, and all analyses were adjusted for age and duration of diabetes. Similar risk factors were found for non-CVD, CVD, unknown-cause, and all-cause mortality (Table 3), with age, A1C, systolic and diastolic blood and pulse pressure, all lipids and lipoproteins, WHR, hypertension, and microvascular complications being the most important. The main difference was that microvascular complications (especially macroalbuminuria, proliferative retinopathy, and autonomic neuropathy) seemed stronger risk factors for CVD mortality than for non-CVD or unknown-cause mortality.

The multivariable Cox proportional hazard models for all-cause mortality were performed, respectively, for risk factors and risk factors plus microvascular complications. Because of the limited number of deaths due to CVD mortality, non-CVD mortality, and unknown-cause mortality, these models were not split by cause of death. From multivariable models, age at baseline (sHR 1.78 [95% CI 1.44–2.20]), WHR (1.32 [1.14–1.52]), pulse pressure (1.33 [1.13–1.58]), and non-HDL cholesterol (1.33 [1.12–1.60]) were important risk factors for all-cause mortality. A1C (1.18 [0.95–1.46]) did not predict mortality independently any longer. Microvascular complications were studied by comparing models of progressive complexity, first one model with complications only and then a model with both complications and risk factors. The model with all complications, retinopathy, albuminuria (AER), and peripheral neuropathy, showed that peripheral neuropathy (2.75 [1.60–4.75]) and albuminuria (1.71 [1.39–2.10]), but not retinopathy (1.29 [0.69–2.39]), were significantly independently related to all-cause mortality. The model including all microvascular complications as well as risk factors (age, A1C, pulse pressure, WHR, and non-HDL cholesterol showed that albuminuria (1.58 [1.26–1.98]) and peripheral neuropathy (1.88 [1.06–3.35]) exceeded the value of the traditional risk factors in their association with all-cause mortality. These analyses were

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Table 3—*Age and duration of diabetes-adjusted analyses between risk factors, microvascular complications, and mortality*

	sHR (95%CI)			
	Non-CVD causes	CVD mortality	Unknown cause	All-cause mortality
n	38	29	35	102
Age at baseline (years)	1.94 (1.42–2.66)	1.72 (1.03–2.86)	2.05 (1.29–3.23)	1.87 (1.44–2.45)
Age at diabetes diagnosis (years)	1.70 (1.32–2.19)	1.54 (1.03–2.31)	1.77 (1.23–2.55)	1.65 (1.33–2.04)
Duration of diabetes (years)	1.06 (0.80–1.42)	1.60 (1.03–2.50)	1.16 (0.77–1.75)	1.20 (0.94–1.53)
A1C (%)*	1.25 (0.99–1.58)	1.42 (0.98–2.05)	1.34 (0.96–1.86)	1.30 (1.07–1.58)
Systolic blood pressure (mmHg)	1.48 (1.22–1.80)	1.43 (1.05–1.95)	1.57 (1.20–2.05)	1.46 (1.24–1.73)
Diastolic blood pressure (mmHg)	1.24 (0.99–1.54)	1.34 (0.94–1.89)	1.42 (1.05–1.94)	1.26 (1.05–1.52)
Pulse pressure (mmHg)	1.37 (1.14–1.64)	1.26 (0.93–1.72)	1.35 (1.04–1.76)	1.34 (1.14–1.57)
Cholesterol (mmol/l)	1.38 (1.12–1.71)	1.14 (0.79–1.64)	1.53 (1.15–2.04)	1.31 (1.09–1.58)
LDL cholesterol (mmol/l)	1.28 (0.99–1.66)	1.37 (0.95–1.99)	1.42 (1.01–1.98)	1.32 (1.06–1.63)
HDL cholesterol (mmol/l)	0.74 (0.58–0.96)	0.61 (0.40–0.92)	0.68 (0.46–1.00)	0.70 (0.56–0.87)
Fasting triglycerides (mmol/l)*	1.34 (1.04–1.73)	1.68 (1.16–2.43)	1.45 (1.03–2.02)	1.44 (1.17–1.78)
Non-HDL cholesterol (mmol/l)	1.45 (1.18–1.77)	1.31 (0.94–1.81)	1.60 (1.21–2.11)	1.40 (1.18–1.67)
Waist-to-hip ratio	1.33 (1.12–1.57)	1.35 (1.06–1.73)	1.15 (0.84–1.56)	1.34 (1.17–1.54)
BMI (kg/m^2)	0.90 (0.71–1.14)	1.03 (0.71–1.51)	0.84 (0.59–1.19)	0.93 (0.76–1.14)
Insulin dose (units · day^{-1} · kg^{-1})	0.83 (0.64–1.07)	1.05 (0.69–1.59)	0.83 (0.57–1.21)	0.88 (0.70–1.09)
AER (μg/min)*	1.60 (1.34–1.91)	2.22 (1.70–2.91)	1.63 (1.27–2.10)	1.75 (1.51–2.03)
Current smoking	1.34 (0.82–2.19)	0.94 (0.39–2.23)	1.24 (0.60–2.57)	1.23 (0.80–1.88)
Low physical activity	1.14 (0.60–2.15)	0.83 (0.39–1.76)	2.63 (1.25–5.50)	1.36 (0.92–2.02)
2–3 insulin injections/day vs. 1 injection	0.72 (0.29–1.80)	0.39 (0.13–1.16)	0.61 (0.19–2.02)	0.58 (0.29–1.15)
Hypertension	2.22 (1.35–3.63)	3.22 (1.42–7.30)	3.01 (1.46–6.20)	2.44 (1.61–3.72)
Antihypertensive medication	2.09 (0.95–4.62)	3.99 (1.84–8.65)	3.91 (1.91–7.99)	3.15 (2.04–4.85)
Microalbuminuria	1.40 (0.82–2.40)	0.76 (0.29–2.04)	1.10 (0.49–2.44)	1.20 (0.75–1.92)
Macroalbuminuria	3.12 (1.78–5.45)	8.73 (4.03–19.0)	3.31 (1.53–7.17)	4.27 (2.75–6.64)
Albuminuria	2.53 (1.55–4.12)	4.51 (1.94–10.5)	2.21 (1.11–4.42)	2.94 (1.93–4.46)
Non-proliferative retinopathy	0.83 (0.46–1.51)	0.78 (0.28–2.19)	0.84 (0.36–1.97)	0.82 (0.49–1.37)
Proliferative retinopathy	2.77 (1.36–5.63)	7.29 (2.22–23.9)	2.53 (0.94–6.81)	3.58 (1.97–6.51)
Retinopathy	1.73 (0.87–3.42)	6.27 (1.29–30.5)	1.72 (0.64–4.66)	2.23 (1.21–4.12)
Autonomic neuropathy: *1*)†	2.81 (1.35–5.83)	3.61 (1.49–8.76)	2.44 (1.20–4.95)	2.83 (1.82–4.38)
Autonomic neuropathy: *2*)†	2.73 (0.81–9.24)	3.71 (1.23–11.2)	1.36 (0.32–5.77)	2.45 (1.21–4.96)
Peripheral neuropathy	3.48 (1.72–7.06)	2.24 (1.00–5.04)	2.76 (1.34–5.71)	2.83 (1.84–4.34)
Cardiovascular disease	0.83 (0.29–2.40)	3.20 (1.42–7.20)	3.93 (1.91–8.10)	2.38 (1.50–3.77)

*Log-transformed corrected A1C values according to the Diabetes Control and Complications Trial method. Cox proportional hazards analyses were performed, with baseline age and diabetes duration adjustments. †Autonomic neuropathy was defined in two ways: *1*) loss of heart rate variability with an RR ratio of <1.04 and/or postural hypotension with a fall in systolic blood pressure of ≥20 mmHg or *2*) loss of heart rate variability with an RR ratio of <1.04 and postural hypotension with a fall in systolic BP of ≥30 mmHg.

repeated with the most severe microvascular complications: proliferative retinopathy, macroalbuminuria, and autonomic neuropathy (definition 1). A model with these severe microvascular complications showed that proliferative retinopathy (2.46 [1.31–4.60]), autonomic neuropathy (definition 1) (3.27 [1.83–5.82]), and macroalbuminuria (3.21 [1.69–6.10]) were all significantly related to all-cause mortality. Adding in the risk factors showed that autonomic neuropathy (definition 1) (2.40 [1.32–4.36]) and macroalbuminuria (2.34 [1.19–4.78]), but not proliferative retinopathy, were independent risk markers that exceeded the value of the traditional risk factors (age, WHR, pulse pressure, and non-HDL cholesterol). Further analyses were carried out adjusting for antihypertensive medication, which is a confounder by indication. These adjusted analyses yielded similar hazard ratios and risk factors as shown above. Those reporting antihypertensive medication were the high-risk type 1 diabetic patients with a subsequently higher risk of all-cause mortality (as shown in Table 3). Splitting these analyses by type of antihypertensive medication (ACE inhibitors, calcium channel antagonists, β-blockers, [thiazide] diuretics, and α-blockers as listed in Table 2) showed that most reported medications were ACE inhibitors.

The final models were expanded with adjustments for low physical activity and baseline CVD, but none of the above-mentioned results were altered, with sHRs of 2.35 [95% CI 1.29–4.28] and 2.39 [1.18–4.83] for autonomic neuropathy and macroalbuminuria, respectively, in a full model including proliferative retinopathy, age, A1C, WHR, pulse pressure, non-HDL cholesterol, low physical activity (1.02 [0.59–1.80]), and baseline CVD (1.23 [0.58–2.59]). Lastly, an interaction between peripheral and autonomic neuropathy was tested to examine the synergistic effect on mortality, but this yielded nonsignificant results ($P = 0.07$).

CONCLUSIONS — Important risk factors for all-cause mortality in patients with type 1 diabetes are age, WHR, pulse pressure, and non-HDL cholesterol. Albuminuria, especially macroalbuminuria, and peripheral and autonomic neuropa-

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thy are important risk markers for all-cause mortality, exceeding the effect of the traditional risk factors. Similar risk factors were found for non-CVD mortality, CVD mortality, unknown-cause, and all-cause mortality.

Mortality is high in patients with type 1 diabetes compared with those without diabetes: in the EURODIAB PCS, 5 deaths per 1,000 person-years were found. In a comparable U.K. general population of the same age-group and no diabetes, death rates are ~0.2–0.5 per 1,000 person-years (1,2). The all-cause mortality rates (per 1,000 person-years) of 5.8 in men and 3.6 in women in the EURODIAB PCS are comparable with other data. These rates are higher than those found in the Diabetes U.K. cohort study (3.4 per 1,000 person-years in men and 2.6 in women) (1) but lower than those found in the London cohort of the World Health Organization (WHO) Multinational Study of Vascular Disease in Diabetes (12.6 in men and 14.3 in women) (20). These differences are consistent with a long-term declining trend in mortality rates among people with type 1 diabetes (21). The most likely explanation for this trend is improved glycemic therapy and antihypertensive therapy management with a resulting decline in morbidity.

The EURODIAB PCS, a clinic-based study with a large sample size, provides a useful Europe-wide summary as the same standardized methods were used in each center. However, there are some limitations. Referral bias and survival bias are the main limitations that cannot be entirely avoided, but the extent is reduced owing to mortality rates comparable with those of other populations. In the epoch in which the cohort was recruited, all those with type 1 diabetes were referred to a hospital clinic, reducing the extent of referral bias. Our analyses were focused on risk factor associations with mortality, and it is highly unlikely that referral bias could sufficiently alter relationships between risk factors and mortality. For example, it is difficult to postulate a reasonable hypothesis that would explain why, for example, a greater WHR increases mortality risk in those referred to our clinics but reduces mortality risk in those somehow not referred. This study was designed primarily as a study of macro- and microvascular disease, and factors more pertinent to conditions such as cancer were not collected. Unfortunately, the number of cigarettes smoked was not collected at baseline, and therefore we could not calculate smoking pack-years. Smoking, classified as current smoker, ex-smoker, or nonsmoker, was not a significant risk factor in our analysis, not even in univariate analyses. Similarly, for BMI, there was no significant univariate association with mortality. Although BMI is still within the normal range, possibly explaining lack of a relationship, other reasons for the absence of these associations remain to be explored. In addition, those lost-to-follow-up, although a relatively small proportion (14%) of the total study population, had a more atherogenic profile in terms of neuropathy, use of antihypertensive medication, and smoking than those included. This could mean that we have underestimated the number of deaths for both men and women. However, the key analysis of the relations between risk factors and mortality is unlikely to be affected, as there is no reason to assume that these relations differ between responders and nonresponders in the study. Although this is the largest type 1 diabetic cohort study available, we had limited power to further analyze multivariate risk factors by specified causes of death or to stratify the analyses by sex because of the limited number of deaths.

Three prospective cohort studies in type 1 diabetes with published data on risk factors for all-cause mortality will be discussed in more detail. Rossing et al. (6) studied 886 patients with type 1 diabetes from an outpatient diabetic clinic in Denmark in 1984, of whom 183 died during 10-years of follow-up. The main independent risk factors for all-cause mortality were sex, age, height, smoking, social class, AER, hypertension, serum creatinine, and A1C. In the WHO Multinational Study of Vascular Disease in Diabetes (5), 1,188 (relatively older) patients with type 1 diabetes were examined during 9 years of follow-up. Proteinuria was found to be an important independent risk factor for all-cause mortality, but no other risk factors were examined. In the Epidemiology of Diabetes Complications (EDC) Study in Pittsburgh (4), 658 patients with type 1 diabetes were examined during 10 years of follow-up, with 68 deaths in total. Ischemic electrocardiogram, duration of diabetes, previous CHD, nephropathy, A1C, serum creatinine, non-HDL cholesterol, and smoking were important independent predictors of mortality. Although the majority of these results are comparable with what we have found, WHR, lipids, and pulse pressure were not taken into account (5,6). The baseline age and duration of diabetes of the different cohort populations differed, with mean baseline age and duration of, respectively, 38 and 21 years in the Danish study (5), 44 and 15 years in the WHO study (4), and 27 and 19 years in the EDC study (6) compared with 32 and 14 years in our EURODIAB PCS cohort. We confirmed the strong independent relationship of albuminuria (or albumin excretion rate) with all-cause mortality in patients with type 1 diabetes (4–6).

Autonomic neuropathy (13) and peripheral neuropathy (10) were important independent risk markers of mortality in the EURODIAB PCS. A meta-analysis (22) as well as the EDC study (23) showed that diabetic autonomic neuropathy was associated with a fourfold increase in mortality. In the EDC study, adjustment for duration of diabetes and presence of CHD lowered this risk to 2.1-fold. After further adjustment for hypertension and nephropathy, the mortality risk associated with diabetic autonomic neuropathy was no longer statistically significant (23). We found HRs of magnitude similar to those reported in these previous studies, which in our larger cohort were robust to adjustment for other risk factors. Previously it was shown that peripheral neuropathy was related to mortality in diabetic patients but not specifically to type 1 diabetes (24,25).

In a previous study we had found retinopathy, especially proliferative retinopathy, to be an important marker for future mortality (26). The additional adjustment for other microvascular complications reduced these findings to nonsignificance, implying that the effects of albuminuria and neuropathy exceed the effect of retinopathy.

All of the microvascular complications were especially strong risk markers in the multivariable models, exceeding the effect of traditional risk factors. The implication of this finding is that treatment of microvascular complications as early as possible is highly recommended to prevent early mortality.

In summary, this large study supports evidence for baseline age, WHR, pulse pressure, and non-HDL cholesterol being important risk factors for all-cause as well as non-CVD mortality in patients with type 1 diabetes. Macroalbuminuria and peripheral and autonomic neuropathy are strong risk markers for mortality.

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APPENDIX

The EURODIAB Prospective Complications Study Group: B. Karamanos, A, Kofinis, and K. Petrou, Hippokration Hospital, Athens, Greece; F. Giorgino, G. Picca, A. Angarano, G. De Pergola, L. Laviola, and R. Giorgino, Medicina Interna, Endocrinologia e Malattie Metaboliche, DETO, Università Degli Studi di Bari, Bari, Italy; M. Songini, A. Casu, M. Pedron, S. Pintus, and M. Fossarello, Department of Internal Medicine, Ospedale San Michele, Cagliari, Italy; J.B. Ferriss, G. Grealy, and D. O Keefe, Cork Regional Hospital, Cork, Ireland; M. Toeller and C. Arden, Diabetes Research Institute, Heinrich-Heine University, Dusseldorf, Germany; R. Rottiers, C. Tuyttens, and H. Priem, University Hospital of Gent, Gent, Belgium; P. Ebeling, M. Kylliäinen, and V.A. Koivisto, University Hospital of Helsinki, Helsinki, Finland; B. Idzior-Walus, J, Sieradzki, and K. Cyganek, Department of Metabolic Diseases, Jagiellonian University, Krakow, Poland; H.H.P.J. Lemkes and J.C. Lemkes-Stuffken, Leiden University Medical Centre, Leiden, the Netherlands; J. Nunes-Correa, M.C. Rogado, L. Gardete-Correia, M.C. Cardoso, A. Silva, J. Boavida, and M. Machado Sa Marques, Portuguese Diabetic Association, Lisbon, Portugal; G. Michel, R. Wirion, and S. Cardillo, Centre Hospitalier, Luxembourg; G. Pozza, R. Mangili, and V. Asnaghi, Ospedale San Raffaele, Milan, Italy; E. Standl, B. Schaffler, H. Brand, and A. Harms, City Hospital Schwabing, Munich, Germany; B. Soussan, O. Verier-Mine, P. Fallas, and M.C. Fallas, Centre Hospitalier de Valenciennes, France; J.H. Fuller, J. Holloway, L. Asbury, and D.J. Betteridge, University College London, London, U.K.; G. Cathelineau, A. Boullouche, and B. Villatte Cathelineau, Hospital Saint-Louis, Paris, France; F. Santeusanio, G. Rosi, V. D'Alessandro, C. Cagini, P. Bottini, and P. Reboldi, Instituto di Patologia Medica, Policlinico, Perugia, Italy; R. Navalesi, G. Penno, S. Bandinelli, R. Miccoli, and M. Nannipieri, Dipartimento di Endocrinologia e Metabolismo, Pisa, Italy; G. Ghirlanda, C. Saponara, P. Cotroneo, A. Manto, and A. Minnella, Universita Cattolica del Sacro Cuore, Rome, Italy; J.D. Ward, S. Tesfaye, S. Eaton, and C. Mody, Royal Hallamshire Hospital, Sheffield, U.K.; M. Borra, P. Cavallo Perin, S. Giunti, G. Grassi, G.F. Pagano, M. Porta, R. Sivieri, F. Vitelli, and D. Ferrari, Dipartimento di Medicina Interna, Università di Torino and ASO CTO/CRF/Maria Adelaide, Turin, Italy; N. Papazoglou and G. Manes, General Hospital of Thessaloniki, Thessaloniki, Greece; M. Muggeo and M. Iagulli, V. Cattedra di Malattie del Metabolismo, Verona, Italy; K. Irsigler and H. Abrahamian, Hospital Vienna Lainz, Vienna, Austria; S. Walford, J. Sinclair, S. Hughes, V. McLelland, and J. Ward, New Cross Hospital, Wolverhampton, U.K.; G. Roglic, Z. Metelko, Z.R. Pepeonik, and Z. Babic, Vuk Vrhovac Institute for Diabetes, Zagreb, Croatia; and C. Ionescu-Tirgoviste, A. Coszma, and C. Guja, Clinic of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania.

Steering Committee members: J.H. Fuller (London), B. Karamanos, Chairman (Athens), A.-K. Sjolie (Aarhus), N. Chaturvedi (London), M. Toeller (Dusseldorf), G. Pozza, Cochairman (Milan), B. Ferriss (Cork), M. Porta (Turin), R. Rottiers (Gent), and G. Michel (Luxembourg).

Coordinating center: J.H. Fuller, N. Chaturvedi, J. Holloway, D. Webb, L. Asbury, M. Shipley, and S.J. Livingstone, University College London.

Central laboratories: G.-C. Viberti, R. Swaminathan, P. Lumb, A. Collins, S. Sankaralingham, and M.A. Crook, Guy's and St. Thomas Hospital, London, U.K.

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