Risk Factors for Coronary Heart Disease in Type 1 Diabetic Patients in Europe

The EURODIAB Prospective Complications Study

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OBJECTIVE — The goal of the study was to examine risk factors in the prediction of coronary heart disease (CHD) and differences in men and women in the EURODIAB Prospective Complications Study.

RESEARCH DESIGN AND METHODS — Baseline risk factors and CHD at follow-up were assessed in 2,329 type 1 diabetic patients without prior CHD. CHD was defined as physician-diagnosed myocardial infarction, angina pectoris, coronary artery bypass graft surgery, and/or Minnesota-coded ischemic electrocardiograms or fatal CHD.

RESULTS — There were 151 patients who developed CHD, and the 7-year incidence rate was 8.0 (per 1,000 person-years) in men and 10.2 in women. After adjustment for age and/or duration of diabetes, the following risk factors were related to CHD in men: age, GHb, waist-to-hip ratio (WHR), HDL cholesterol, smoking, albumin excretion rate (AER), and autonomic neuropathy. The following risk factors were related to CHD in women: age, systolic blood pressure (BP), fasting triglycerides, AER, and retinopathy. Multivariate standardized Cox proportional hazards models showed that age (hazard ratio 1.5), AER (1.3 in men and 1.6 in women), WHR (1.3 in men), smoking (1.5 in men), fasting triglycerides (1.3 in women) or HDL cholesterol (0.74 in women), and systolic BP (1.3 in women) were predictors of CHD.

CONCLUSIONS — This study supports the evidence for a strong predictive role of baseline albuminuria in the pathogenesis of CHD in type 1 diabetes. Furthermore, sex-specific risk factors such as systolic BP, fasting triglycerides (or HDL cholesterol), and WHR were found to be important in the development of CHD.

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Type 1 diabetes is associated with a four- (in men) to eightfold (in women) excess risk of coronary heart disease (CHD) (1,2). This substantially elevated risk in women with diabetes effectively obliterates the sex difference in CHD observed in the general population (3,4).

Established risk factors do not appear to account for the excess risk of CHD in type 1 diabetes, and reasons for the greater impact in women are not clear. But there is a lack of large prospective studies in type 1 diabetic patients. Much of the research into CHD risk in diabetes has focused on type 2 diabetes and insulin resistance. Type 1 diabetes has a different pathogenesis from type 2 diabetes, and although there are similarities between the diseases such as hyperglycemia, inferences cannot be made from one type to the other for all risk factors, such as lipids and obesity. For example, type 1 diabetes is associated with a favorable lipid pattern compared with the general population, which is clearly not true for type 2 diabetes (5).

Previous studies of type 1 diabetic patients suggest that albuminuria (4,6–9) and raised blood pressure (BP) (4,6–9) are important risk factors for CHD, but these studies had insufficient power to stratify analyses by sex. The case for an independent relationship between obesity measures and CHD is unclear, the role of the other complications of diabetes uncertain, and findings for lipid and lipoprotein concentrations in relation to CHD are conflicting (8,9).

Therefore, we explored the role of conventional and diabetes-specific risk factors in the incidence of CHD in a large European sample of type 1 diabetic patients and the differences in risk factors between men and women.

RESEARCH DESIGN AND METHODS

— Full details of the design, methods, and recruitment in the EURODIAB Prospective Complications Study (PCS) have been published elsewhere (10–12). The baseline cross-sectional clinic-based study examined 3,250 type 1 diabetic patients between 1989–1991. Participants were aged between 15 and 60 years and recruited from 31 centers in 16 European countries. The sampling frame was all type 1 diabetic patients attending at least once in the last year for each center. Patients were stratified by age (three categories), diabetes du-

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Abbreviations: AER, albumin excretion rate; BP, blood pressure; CHD, coronary heart disease; ECG, electrocardiogram; EDC, epidemiology of diabetes complications; FTG, fasting triglycerides; MI, myocardial infarction; PCS, Prospective Complications Study; WHR, waist-to-hip ratio.

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

ration (three categories), and sex. Ten patients were then randomly selected from each stratum (10). 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 a 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 re-examination. Of the 3,250 subjects at baseline, 681 individuals could not be assessed or were excluded from follow-up because of the following reasons. Eight patients did not meet the inclusion criteria at baseline, 222 patients had CHD at baseline, and in 14 patients, CHD was not measured. In addition, four centers (n = 437) did not participate in the follow-up examination. Of the remaining 2,569 subjects, 2,329 could be assessed for CHD, of which 151 had CHD at follow-up and 2,178 did not.

Measurements

All risk factors and microvascular complications were measured at baseline according to a standardized protocol (11). BP was recorded in a sitting position with a random zero sphygmomanometer (Hawskley, Lancing, U.K.) as the mean of two measurements. Hypertension was defined as a systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg and/or the current use of BP-lowering drugs.

Retinopathy was assessed by retinal photographs taken according to the EURODIAB protocol (13). Grading was performed by the Retinopathy Grading Centre at the Hammersmith Hospital, Imperial College London. Retinopathy was classified as none (level 0), nonproliferative (levels 1–3), and proliferative retinopathy (levels 4 and 5).

Peripheral neuropathy was assessed on the basis of neuropathic symptoms and signs, including measurement of vibration perception threshold. Autonomic neuropathy was defined as an R-R ratio of <1.04 and/or a fall in BP from resting to standing of >20 mmHg (14).

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 dipstick test for bacteria. Urinary albumin was measured in a single laboratory by an immunoturbidimetric method (Sanofi Diagnostics Pasteur, Minneapolis, MN) (15). AER was categorized as normoalbuminuria at ≤20 μg/min, microalbuminuria between 20 and 200 μg/min, and macroalbuminuria at ≥200 μg/min. Albuminuria was defined as micro- and macroalbuminuria. A blood sample was taken for the measurement of plasma lipids (fasting triglycerides [FTG], cholesterol, HDL cholesterol) and GHb. Triglyceride (16) and cholesterol (17) concentration of plasma and the cholesterol concentration of HDL (18) 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, 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 below 400 mg/dl (19). Fifteen patients did not have their LDL cholesterol calculated. Non-HDL cholesterol was calculated as HDL cholesterol subtracted from total cholesterol.

The value of GHb was measured centrally by an enzyme immunoassay (Dako, Ely, U.K.) using a monoclonal antibody raised against GHb with a reference range of 2.9–4.8% (20). The intra-assay and interassay coefficients of variation were 2.3–2.4% and 2.6–5.0%, respectively.

Outcome

CHD (follow-up) was defined as a previous physician diagnosis of CHD or presence of electrocardiogram (ECG) abnormalities. The former included: myocardial infarction (MI), angina pectoris, or coronary artery bypass graft surgery. A conventional 12-lead resting ECG was recorded on each subject. ECG abnormalities were classified by two observers according to the Minnesota Code (21). Any discrepancies between the two observers were adjudicated by a third. ECG abnormalities suggestive of probable ischemia consist of codes 1.1 and 1.2 (major Q/QS waves) and code 7.1 (complete left bundle branch block). Possible ischemia consists of code 1.3 for minor Q waves, codes 4.1, 4.2, and 4.3 for ST segment abnormalities, and codes 5.1, 5.2, and 5.3 for T wave abnormalities. Death due to CHD causes was also included and coded according to ICD-9 (410–414) classification.

All CHD events were captured by questionnaire with additional supporting information from hospital records, death certificates, and other health care documents. In addition, a comparison of allocation of cause of death was performed separately by two observers (J.H.F. and N.C.) with 100% agreement.

Statistical analysis

The statistical packages SAS (version 8.0; SAS, Cary, NC) and STATA 7 were used to perform all analyses. Descriptive statistics were performed to estimate differences between subjects; Student's t test and χ^2 test were used as appropriate. Spearman's rank correlations were used to test the cross-sectional relationship between risk factors. Non-normally distributed variables were log transformed.

Incidence rates (per 1,000 person-years) for CHD were calculated by sex and age-group.

Sex differences in risk factors were tested by fitting interaction terms between specific risk factors with sex using data on the whole study population. Interactions were only tested for risk factors that were thought to be different between men and women, such as waist-to-hip ratio (WHR) (P = 0.03 in a model with WHR, sex, and an interaction term of WHR and sex), smoking (P = 0.14), and AER (P = 0.19). Furthermore, sex-specific variables were analyzed simultaneously to estimate which risk factors were more important in men and in women. Sex-specific variables were defined by nesting each variable for men and women separately (for example WHR × [sex = 1] for men and WHR × [sex = 0] for women). As interactions and sex-specific variables were observed suggestive of a difference between men and women, findings are presented stratified by sex.

Univariate and multivariate Cox proportional hazards modeling were used to estimate hazard ratios for CHD associated with risk factors. A simultaneous and stepwise approach was used to determine the most important risk factors. Likelihood ratio tests were used to estimate the

importance of each risk factor. 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 were estimated from these models by exponentiating the β-coefficient multiplied by the standard deviation (Exp[β × SD]).

RESULTS — Of the 151 CHD events, 34% ($n = 51$) were classified on the basis of physician-diagnosed angina pectoris, coronary artery bypass grafting, and MI; 11% ($n = 17$) were due to fatal CHD; and the rest of the events were assessed on the basis of Minnesota coded ischemic ECGs (possible MI [3%] and probable MI [52%]). CHD events were equally distributed between men and women. CHD incidence rates were higher in women than in men, 10.2 (95% CI 8.2–12.7) compared with 8.0 (6.3–10.1) per 1,000 person-years, but this was not statistically significant ($P = 0.14$). Men and women >40 years of age at baseline had three times higher CHD incidence rates than those <40 years (24 vs. 8 per 1,000 person-years in women and 20 vs. 5 per 1,000 person-years in men) ($P = 0.0001$).

Baseline characteristics between those included and those lost to follow-up

Baseline risk factors were compared between those included ($n = 2,329$) and those lost to follow-up ($n = 921$) for men and women separately (data not shown). A more atherogenic risk factor profile was found in those who dropped out, even when adjusted for age, such as older age and duration of diabetes, worse glycemic control, abnormal lipid levels, higher BP, and more microvascular complications.

Baseline characteristics by CHD status at follow-up

Apart from WHR and smoking, there were no major differences in risk factors for CHD between men and women at baseline (Table 1).

Adjustment for age and duration

After adjustment for diabetes duration, age was a significant risk factor for CHD, whereas diabetes duration, adjusted for age, was not significantly related to CHD (Table 2). Age and diabetes duration were highly correlated (Spearman's correlation coefficient = 0.51).

In men and women, baseline age and increased AER levels were significant risk factors for CHD. In addition in men, current smoking, WHR, and raised levels of GHb predicted CHD, whereas in women, raised systolic BP and increased levels of FTG were significantly and positively related to CHD. Of the other complications, autonomic neuropathy and total neuropathy were significantly related to CHD in men, whereas retinopathy was related to CHD in women. Further adjustment for center did not alter these results.

Multivariate models

The variables that persisted in models with age and diabetes duration adjustment were simultaneously added in multivariate models (Table 3).

In men, baseline age, WHR, and AER were independent predictors of CHD. Current smoking was also related to CHD in men, although it was not statistically significant. Of the other complications, autonomic neuropathy as well as peripheral neuropathy were related to CHD in men with hazard ratios of, respectively, 1.71 (95% CI 1.03–2.85, $P = 0.037$) and 1.68 (1.01–2.77, $P = 0.045$), adjusted for age, WHR, and smoking. Further adjustment for hypertension (in a model with age, WHR, and smoking) still showed strong and hardly unaltered hazard ratios for the association between autonomic neuropathy and CHD (hazard ratio [HR] 1.66, 95% CI 0.99–2.74, $P = 0.051$) and between peripheral neuropathy and CHD (1.70, 1.02–2.82, $P = 0.04$). In all of these models, the significant estimates for age, WHR, and smoking were not affected.

In women, baseline age and AER were the most important predictors of CHD. Systolic BP and FTG increased the risk of CHD, although these associations only reached borderline statistical significance. Retinopathy was related to CHD in women (HR 1.77, 95% CI 0.93–3.37, $P = 0.08$) and was adjusted for age, systolic BP, and FTG but was not statistically significant.

Other possibly important risk factors with a less stringent *P* value of <0.20 (from Table 2) were entered in a forward stepwise manner to estimate independent effects of any additional variables to the models. None of the other variables significantly contributed to the prediction of CHD in men. However, in women, HDL cholesterol (HR 0.74, 95% CI 0.56–0.98) did contribute significantly to the prediction of CHD (independently of age, AER, and systolic BP). Adding in HDL cholesterol made the relationship with FTG disappear due to the high negative correlation between HDL cholesterol and FTG ($r = -0.34$).

Furthermore, Cox proportional hazards models were carried out in the total population (with more statistical power) using sex-specific variables for age, smoking, WHR, systolic BP, FTG, and AER to estimate which risk factors were more important in men and women. In these analyses, WHR was a more important predictor in men than in women ($P = 0.01$ in men compared with $P = 0.2$ in women). Similarly, systolic BP ($P = 0.92$ in men and 0.003 in women) and FTG ($P = 0.82$ in men and 0.003 in women) were significant predictors in women but not in men.

Restriction of the CHD events to hard events (omitting ECG-related events) only, bearing in mind the lack of statistical power, did not alter the results. Adjustment for center and BP- and lipid-lowering drugs in the multivariate models did not alter the results.

CONCLUSIONS — Incidence rates of CHD were substantially higher in this type 1 diabetic population at ~1% per year compared with general population incidence rates of 0.1–0.5% per year in those aged 25–74 years (22,23). This compares favorably with the World Health Organization Multinational Study of Vascular Disease in Diabetes with incidence rates of 1.6 and 1.2% per year in men and women, respectively (9), and 2% per year in the Epidemiology of Diabetes Complications (EDC) study.

Higher CHD incidence rates were found in women compared with men in the EURODIAB PCS. Our study suggests clear differences in risk factors predicting CHD in men compared with women, with WHR (and smoking) more important in men and FTG (or HDL cholesterol) and systolic BP more important in women. The EDC study demonstrated the importance of overt nephropathy, WHR, diabetes duration, hypertension, triglycerides,

Table 1—*Baseline characteristics of the EURODLAB PCS population*

	n	Total CHD$^+$	Total CHD$^-$	Men CHD$^+$	Men CHD$^-$	Women CHD$^+$	Women CHD$^-$
n		151	2,178	69	1,133	82	1,045
Age (years)	2,329	38.1 ± 10.5	31.7 ± 9.5	37.4 ± 10.5	31.8 ± 9.5	38.6 ± 10.6	31.6 ± 9.5
Diabetes duration (years)	2,328	19.0 ± 10.3	14.0 ± 8.8	17.9 ± 10.5	13.7 ± 8.7	19.9 ± 10.1	14.3 ± 9.0
GHb (%)	2,313	6.85 ± 1.63	6.63 ± 1.88	6.98 ± 1.65	6.57 ± 1.84	6.74 ± 1.61	6.69 ± 1.91
Systolic BP (mmHg)	2,321	126.9 ± 19.9	119.7 ± 16.5	127.6 ± 21.4	122.4 ± 16.0	126.2 ± 18.7	116.8 ± 16.5
Diastolic BP (mmHg)	2,321	75.0 ± 11.8	75.0 ± 11.2	75.8 ± 12.3	76.2 ± 11.2	74.4 ± 11.3	73.7 ± 11.0
Cholesterol (mg/dl)	2,303	214.2 ± 46.3	204.8 ± 43.3	208.4 ± 47.4	200.0 ± 42.6	219.2 ± 45.1	210.1 ± 43.4
LDL cholesterol (mg/dl)	1,545	136.0 ± 41.9	128.2 ± 37.4	136.1 ± 44.0	127.0 ± 36.6	136.8 ± 40.9	129.8 ± 38.9
HDL cholesterol (mg/dl)	2,288	56.2 ± 17.0	58.2 ± 16.5	50.7 ± 13.9	53.6 ± 14.9	61.0 ± 18.1	63.2 ± 16.8
Non-HDL cholesterol (mg/dl)	2,288	158.0 ± 47.4	146.6 ± 43.8	157.6 ± 49.6	146.3 ± 43.0	158.2 ± 45.8	146.8 ± 44.7
FTG (mg/dl)	1,565	93.8 (65.2–135.7)	79.5 (60.7–110.7)	100.4 (69.2–143.3)	83.0 (62.5–118.8)	85.7 (63.4–133.0)	76.8 (58.9–100.0)
Waist circumference (cm)	2,318	81.6 ± 10.1	79.4 ± 9.4	86.6 ± 8.5	83.2 ± 8.7	77.4 ± 9.4	75.3 ± 8.5
WHR	2,318	0.86 ± 0.10	0.84 ± 0.10	0.92 ± 0.07	0.88 ± 0.08	0.82 ± 0.10	0.80 ± 0.10
BMI (kg/m^2)	2,312	23.9 ± 2.9	23.5 ± 2.8	24.3 ± 2.8	23.6 ± 2.6	23.6 ± 3.0	23.3 ± 2.9
AER (μg/min)	2,225	20.2 (8.6–87.9)	10.7 (6.5–21.9)	35.9 (9.1–278.2)	11.3 (6.8–25.4)	15.7 (8.5–81.4)	10.1 (6.2–19.8)
Insulin dose (units • day^{-1} • kg^{-1})	2,290	0.64 (0.53–0.77)	0.67 (0.54–0.81)	0.67 (0.53–0.79)	0.66 (0.54–0.81)	0.62 (0.53–0.76)	0.67 (0.55–0.82)
No. of insulin injections/day	2,325	2.37 ± 0.68	2.58 ± 0.75	2.32 ± 0.74	2.54 ± 0.74	2.41 ± 0.63	2.62 ± 0.76
Hypertension (yes)	2,329	34 (51)	21 (450)	35 (24)	23 (256)	33 (27)	19 (194)
BP-lowering drugs (yes)	2,316	18 (27)	7.5 (162)	20 (14)	7.7 (87)	16 (13)	7.2 (75)
Lipid-lowering drugs (yes)	2,322	2.7 (4)	1.2 (27)	4 (3)	1.4 (16)	1.2 (1)	1.1 (11)
Current smoking	2,322	35 (52)	31 (667)	43 (30)	33 (369)	27 (22)	29 (298)
Exsmoking	2,322	17 (25)	18 (389)	22 (15)	21 (242)	12 (10)	14 (147)
Retinopathy*	1,919	64 (74)	44 (790)	62 (36)	46 (435)	67 (38)	41 (355)
Neuropathy	2,284	46 (69)	31 (653)	51 (35)	31 (343)	41 (34)	30 (310)
Autonomic neuropathy	2,162	38 (53)	28 (557)	43 (27)	27 (277)	35 (26)	29 (280)
Microalbuminuria	2,225	31 (44)	20 (427)	33 (20)	22 (241)	30 (24)	19 (186)
Macroalbuminuria	2,225	19 (27)	7.0 (145)	26 (16)	7.7 (83)	14 (11)	6 (62)

Data are means ± SD, median (interquartile range), or % (*n*). *Nonproliferative and proliferative retinopathy.

Table 2—*Cox proportional hazards models with baseline risk factors and incident CHD, age, and diabetes duration adjusted*

	Standardized hazard ratios (95% CI)		
	Total	Men	Women
n	2,329	1,202	1,127
Age (years)*	1.60 (1.30–1.96)‡	1.55 (1.15–2.09)‖	1.67 (1.26–2.21)¶
Diabetes duration (years)*	1.16 (0.95–1.40)	1.12 (0.85–1.49)	1.16 (0.89–1.52)
GHb (%)	1.20 (1.02–1.41)§	1.34 (1.06–1.68)‖	1.07 (0.85–1.35)
Waist circumference (cm)	1.07 (0.92–1.26)	1.19 (0.94–1.52)	1.13 (0.92–1.39)
WHR	1.15 (0.99–1.33) ($P = 0.06$)	1.32 (1.08–1.62)‖	1.16 (0.97–1.39) ($P = 0.11$)
BMI (kg/m^2)	1.05 (0.90–1.23)	1.17 (0.92–1.48)	1.00 (0.81–1.24)
Systolic BP (mmHg)	1.17 (1.01–1.36)§	1.11 (0.88–1.39)	1.26 (1.03–1.54)§
Diastolic BP (mmHg)	0.98 (0.84–1.14)	0.90 (0.71–1.14)	1.08 (0.88–1.34)
Cholesterol (mg/dl)	1.04 (0.88–1.22)	1.04 (0.81–1.33)	1.02 (0.82–1.26)
LDL cholesterol (mg/dl)	1.05 (0.87–1.26)	1.12 (0.83–1.52)	1.00 (0.79–1.26)
HDL cholesterol (mg/dl)	0.82 (0.70–0.97)§	0.75 (0.58–0.97)§	0.82 (0.66–1.02) ($P = 0.08$)
Non-HDL cholesterol (mg/dl)	1.11 (0.96–1.30) ($P = 0.17$)	1.14 (0.90–1.43)	1.09 (0.89–1.34)
FTG (mg/dl)†	1.27 (1.08–1.50)‖	1.26 (0.96–1.64) ($P = 0.10$)	1.36 (1.10–1.69)‖
Current smoking versus nonsmoking	1.30 (0.93–1.83) ($P = 0.13$)	1.62 (1.004–2.62)§	1.08 (0.66–1.78)
Exsmoking versus nonsmoking	0.70 (0.46–1.09) ($P = 0.11$)	0.70 (0.39–1.28)	0.78 (0.40–1.52)
Retinopathy	1.68 (1.09–2.60)§	1.42 (0.77–2.62)	2.02 (1.07–3.82)§
Neuropathy	1.34 (0.95–1.89)	1.77 (1.07–2.95)§	1.07 (0.67–1.72)
Autonomic neuropathy	1.41 (1.00–2.00) ($P = 0.05$)	1.79 (1.08–2.97)§	1.15 (0.71–1.86)
Microalbuminuria	1.65 (1.16–2.37)‖	1.57 (0.91–2.70) ($P = 0.10$)	1.87 (1.16–3.02)‖
Macroalbuminuria	2.74 (1.79–4.19)‡	3.53 (1.97–6.33)‡	2.38 (1.24–4.57)‖
AER (μg/min)†	1.50 (1.32–1.70)‡	1.68 (1.39–2.02)‡	1.43 (1.20–1.71)‡
Hypertension (yes versus no)	1.31 (0.91–1.86) ($P = 0.14$)	1.30 (0.77–2.18)	1.35 (0.83–2.19)

*Age adjusted for diabetes duration and vice versa for diabetes duration. †Log transformed; ‡$P \leq 0.0001$; §$P \leq 0.05$; ‖$P \leq 0.01$; ¶$P \leq 0.001$. Adjustment for center does not change these results. Standardized hazards ratios (Exp[$\beta \times$ SD]).

and HDL cholesterol in predicting CHD, but a sex-specific analysis was not performed (8).

We confirm the strong independent relationship of albuminuria with CHD when compared with other risk factors (4,6–9,24,25).

Some studies have shown that an adverse lipid profile is already present at the microalbuminuric stage (26,27). However, limited results have been published for lipid and lipoprotein concentrations in relation to CHD (8,9). Our findings of independent relationships between FTG or HDL cholesterol and CHD have been reported previously (8), but in the only other large cohort study in type 1 diabetic patients, HDL cholesterol was not measured, and no significant relationship was found between FTG and CHD (9).

Our study showed an independent relationship between WHR and CHD, which was not measured or not found to be related to CHD in most previous studies (4,6,7,9,28,29). However, our findings do agree with the EDC study (30). Possible reasons for the discrepancy in findings could be due to the small sample size in previous studies or simply due to the fact that type 1 diabetic patients are generally lean. Even though type 1 diabetic patients are usually lean, weight gain is associated with intensive glycemic control, which could lead to varying the use of insulin as a method to lose or gain weight (31,32). As in our study, several prospective studies did not find a significant relationship between BMI and CHD, even in univariate analyses (7,8,28), perhaps because BMI is a more general marker of obesity, whereas WHR measures, more specifically, central obesity.

Clustering of risk factors, such as triglycerides, elevated BP, central obesity, and perhaps albuminuria as part of the insulin resistance syndrome (33) could play an important role in the pathogenesis of CHD in type 1 diabetes. This proposal is supported by findings from the EDC (34) where estimated glucose disposal

Table 3—*Multivariate Cox proportional hazards models for men and women separately in the EURODIAB PCS*

	Standardized hazards ratio (95% CI)*	
	Men	Women
n	1,134 (61 events)	730 (68 events)
Age (years)	1.46 (1.15–1.86)‡	1.51 (1.19–1.92)¶
WHR	1.27 (1.02–1.59)§	
Current smoking	1.54 (0.93–2.55) ($P = 0.10$)	
AER (μg/min)†	1.64 (1.36–1.97)‖	1.33 (1.09–1.63)‡
Systolic BP (mmHg)		1.25 (0.99–1.56) ($P = 0.05$)
FTG (mg/dl)†		1.25 (0.99–1.58) ($P = 0.06$)

*Standardized hazards ratios (Exp[$\beta \times$ SD]); †log transformed; ‡$P \leq 0.01$; §$P < 0.05$; ‖$P \leq 0.0001$; ¶$P \leq 0.001$.

rate (a marker for insulin resistance) was prospectively related to lower extremity arterial disease (35).

Conflicting results have been reported regarding the relationship between hyperglycemia and CHD in type 1 diabetic cohort studies, with some studies not finding (6,7,36) and other studies finding (28,37) an independent association. The negative findings reported in our study, which might be due to the difficulty of detecting a statistical difference for GHb values, which are already raised and at the upper end of the distribution, do not imply that optimal glycemic control is not important in the prevention of vascular complications in type 1 diabetes, as clearly demonstrated by the Diabetes Control and Complications Trial (38).

Prior prospective studies in type 1 diabetic patients also showed strong independent associations between elevated BP and CHD (6–9). In the largest of these studies, a higher excess mortality was shown in type 1 than in type 2 diabetic patients, especially when both hypertension and proteinuria were present (39). It is not known, however, whether BP is elevated before the onset of albuminuria or as a consequence of it and further research is needed to explore the pathogenesis (40,41).

In addition to albuminuria, other diabetic complications, such as retinopathy, peripheral, and autonomic neuropathy, were related to the development of CHD. To our knowledge, there are no prospective studies in type 1 diabetic patients that have found strong independent relationships between these complications and CHD. Due to interrelationships with other established risk factors, it was difficult to separate the effects of these other complications and assess independent associations with CHD.

Differences in type 1 and 2 diabetes can be indicated. In type 1 diabetes, important risk factors for CHD are more diabetes-related risk factors, such as albuminuria and other risk factors such as FTG and WHR. In contrast in type 2 diabetes, the more conventional risk factors (smoking, dyslipidemia, and BP) are important (42). CHD and type 2 diabetes are thought to have common antecedents, the so-called "common soil" hypothesis (43), such as hypertension, insulin resistance, and obesity, whereas type 1 diabetes is a state of insulin deficiency.

The EURODIAB PCS, a clinic-based study with a large sample size, provides a useful European-wide summary as the same standardized methods were used in each center. However, there are some limitations. Just over 50% of CHD events were classified by Minnesota- coded ECGs, and a comparison with baseline ECGs was not performed due to the 7-year gap in coding of baseline and follow-up ECGs. Although viewed as a softer end point than, for example, admission to hospital with an acute event, or a bypass graft operation, the former is at least standardized across centers, whereas as access to health care and thresholds for coronary interventions may differ by center, these latter measures may be less useful for a multicenter study of this type than they first appear. Restriction of the CHD events to hard events (omitting ECG-related events) only, bearing in mind the lack of statistical power, did not alter the results. Of the total baseline sample, 28% participants were lost to follow-up. We showed that these individuals were likely to have a more atherogenic profile than participants in the follow-up. This is likely to mean that we have underestimated the incidence of CHD, and that is true for both men and women. However, our key analyses of interest, the relationship between risk factors at baseline and disease at follow-up, are unlikely to be affected, as it is hard to hypothesize a situation where albuminuria is strongly positively associated with events in responders but negatively associated in nonresponders. Multiple testing could have led to more significant results than there actually are; however, careful statistical analysis and interpretations were made. Furthermore, several studies, although smaller, have confirmed similar risk factors as in our study.

In conclusion, this large study supports the evidence for a strong predictive role of baseline albuminuria in the pathogenesis of CHD in type 1 diabetes. Furthermore, sex-specific risk factors such as systolic BP, FTG (or HDL cholesterol), and WHR were found to be important in the development of CHD and need to be explored further.

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References

1. Swerdlow AJ, Jones ME: Mortality during 25 years of follow-up of a cohort with diabetes. *Int J Epidemiol* 25:1250–1261, 1996
2. Laing SP, Swerdlow AJ, Slater SD, Bothat JL, Burden AC, Waugh NR, Smith AW, Hill RD, Bingley PJ, Patterson CC, Qiao Z, Keen H: The British Diabetic Association Cohort Study II: cause-specific mortality in patients with insulin-treated diabetes mellitus. *Diabet Med* 16:466–471, 1999
3. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL: Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men: the Rancho Bernardo Study *JAMA* 265:627–631, 1991 [published erratum appears in *JAMA* 265:3249, 1991]
4. Krolewski AS, Kosinski EJ, Warram JH, Leland OS, Busick EJ, Asmal AC, Rand LI, Christlieb AR, Bradley RF, Kahn CR: Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. *Am J Cardiol* 59:750–755, 1987
5. Taskinen M-R: Quantitative and qualitative lipoprotein abnormalities in diabetes mellitus. *Diabetes* 41:12–17, 1993
6. Rossing P, Hougaard P, Borch-Johnsen K, Parving HH: Predictors of mortality in insulin dependent diabetes: 10 year observational follow up study. *BMJ* 313:779–784, 1996
7. Deckert T, Yokoyama H, Mathiesen E, Ronn B, Jensen T, Feldt RB, Borch-Johnson K, Jensen JS: Cohort study of predictive value of urinary albumin excretion for atherosclerotic vascular disease in patients with insulin dependent diabetes. *BMJ* 312:871–874, 1996
8. Forrest KY, Becker DJ, Kuller LH, Wolfson SK, Orchard TJ: Are predictors of coronary heart disease and lower-extremity arterial disease in type 1 diabetes the same: a prospective study. *Atherosclerosis* 148:159–169, 2000
9. Fuller JH, Stevens LK, Wang SL: Risk factors for cardiovascular mortality and morbidity: the WHO Mutinational Study of Vascular Disease in Diabetes. *Diabetologia* 44 (Suppl. 2):S54–S64, 2001
10. EURODIAB IDDM Complications Study Group: Microvascular and acute complications in IDDM patients: the EURODIAB IDDM Complications Study. *Diabetologia* 37:278–285, 1994
11. Koivisto VA, Stevens LK, Mattock M, Ebeling P, Muggeo M, Stephenson J, Idzior WB: Cardiovascular disease and its risk factors in IDDM in Europe: EURODIAB IDDM Complications Study Group. *Diabetes Care* 19:689–697, 1996
12. Chaturvedi N, Sjoelie AK, Porta M, Aldington SJ, Fuller JH, Songini M, Kohner EM, the EURODIAB Prospective Complications Study Group: Markers of insulin resistance are strong risk factors for retinopathy incidence in type 1 diabetes. *Diabetes Care* 24:284–289, 2001
13. Aldington SJ, Kohner EM, Meuer S, Klein R, Sjolie AK: Methodology for retinal photography and assessment of diabetic retinopathy: the EURODIAB IDDM complications study. *Diabetologia* 38:437–444, 1995
14. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology: Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *Neurology* 46: 1470, 1996
15. Kearney EM, Mount JN, Watts GF, Slavin BM, Kind PR: Simple immunoturbidimetric method for determining urinary albumin at low concentrations using Cobas-Bio centrifugal analyser. *J Clin Pathol* 40: 465–468, 1987
16. Bucolo G, David H: Quantitative determination of serum triglycerides by the use of enzymes. *Clin Chem* 19:476–482, 1973
17. Siedel J, Hagele EO, Ziegenhorn J, Wahlefeld AW: Reagent for the enzymatic determination of serum total cholesterol with improved lipolytic efficiency. *Clin Chem* 29:1075–1080, 1983
18. Warnick GR, Albers JJ: A comprehensive evaluation of the heparin-manganese precipitation procedure for estimating high density lipoprotein cholesterol. *J Lipid Res* 19:65–76, 1978
19. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
20. John WG, Gray MR, Bates DL, Beacham JL: Enzyme immunoassay: a new technique for estimating hemoglobin A1c. *Clin Chem* 39:663–666, 1993
21. Prineas RJ, Crow RS, Blackburn H: *The Minnesota Code Manual of Electrocardiographic Findings*. Littleton, MA, John Wright, 1982
22. Tunstall-Pedoe H, Vanuzzo D, Hobbs M, Mahonen M, Cepaitis Z, Kuulasmaa K, Keil U: Estimation of contribution of changes in coronary care to improving survival, event rates, and coronary heart disease mortality across the WHO MONICA Project populations. *Lancet* 355:688–700, 2000
23. Ducimetiere P, Ruidavets JB, Montaye M, Haas B, Yarnell J: Five-year incidence of angina pectoris and other forms of coronary heart disease in healthy men aged 50–59 in France and Northern Ireland: the Prospective Epidemiological Study of Myocardial Infarction (PRIME) Study. *Int J Epidemiol* 30:1057–1062, 2001
24. Borch-Johnsen K, Kreiner S: Proteinuria: value as predictor of cardiovascular mortality in insulin dependent diabetes mellitus. *Br Med J Clin Res Ed* 294:1651–1654, 1987
25. Jensen T, Borch-Johnson K, Kofoed EA, Deckert T: Coronary heart disease in young type 1 (insulin-dependent) diabetic patients with and without diabetic nephropathy: incidence and risk factors. *Diabetologia* 30:144–148, 1987
26. Jones SL, Close CF, Mattock MB, Jarrett RJ, Keen H, Viberti GC: Plasma lipid and coagulation factor concentrations in insulin dependent diabetics with microalbuminuria. *BMJ* 298:487–490, 1989
27. Groop PH: Lipidaemia and diabetic renal disease. In *The Kidney and Hypertension in Diabetes Mellitus*. 4th ed. Mogensen CE, Ed. 1998, p. 357–369
28. Lehto S, Ronnemaa T, Pyorala K, Laakso M: Poor glycemic control predicts coronary heart disease events in patients with type 1 diabetes without nephropathy. *Arterioscler Thromb Vasc Biol* 19:1014–1019, 1999
29. Klein R, Klein BE, Moss SE, Cruickshanks KJ: Association of ocular disease and mortality in a diabetic population. *Arch Ophthalmol* 117:1487–1495, 1999
30. Lloyd CE, Kuller LH, Ellis D, Becker DJ, Wing RR, Orchard TJ: Coronary artery disease in IDDM: gender differences in risk factors but not risk. *Arterioscler Thromb Vasc Biol* 16:720–726, 1996
31. Diabetes Control and Complications Trial Research Group: Influence of intensive diabetes treatment on body weight and composition of adults with type 1 diabetes in the Diabetes Control and Complications Trial. *Diabetes Care* 24:1711–1721, 2001
32. Williams KV, Erbey JR, Becker D, Orchard TJ: Improved glycemic control reduces the impact of weight gain on cardiovascular risk factors in type 1 diabetes: the Epidemiology of Diabetes Complications Study. *Diabetes Care* 22:1084–1091, 1999
33. Reaven GM: Banting Lecture 1988: role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
34. Williams KV, Erbey JR, Becker D, Arslanian S, Orchard TJ: Can clinical factors

estimate insulin resistance in type 1 diabetes? *Diabetes* 49:626–632, 2000
35. Olson JC, Erbey JR, Forrest KY, Williams K, Becker DJ, Orchard TJ: Glycemia (or, in women, estimated glucose disposal rate) predict lower extremity arterial disease events in type 1 diabetes. *Metabolism* 51:248–254, 2002
36. Orchard TJ, Olson JC, Erbey JR, Williams K, Forrest KY, Smithline KL, Ellis D, Becker DJ: Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes: 10-year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care* 26:1374–1379, 2003
37. Klein R: Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 18:258–268, 1995
38. 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: the Diabetes Control and Complications Trial Research Group. *N Engl J Med* 329:977–986, 1993
39. Wang SL, Head J, Stevens L, Fuller JH: Excess mortality and its relation to hypertension and proteinuria in diabetic patients: the World Health Organization Multinational Study of Vascular Disease in Diabetes. *Diabetes Care* 19:305–312, 1996
40. Christiansen JS: Glomerular hyperfiltration in diabetes mellitus. *Diabet Med* 2: 235–239, 1985
41. Mogensen CE, Hansen KW, Osterby R, Damsgaard EM: Blood pressure elevation versus abnormal albuminuria in the genesis and prediction of renal disease in diabetes. *Diabetes Care* 15:1192–1204, 1992
42. Stamler J, Vaccaro O, Neaton JD, Wentworth D, Mutiple Risk Factor Intervention Trial Research Group: Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the multiple risk factor intervention trial. *Diabetes Care* 16:434–444, 1993
43. Stern MP: Diabetes and cardiovascular disease: the "common soil" hypothesis. *Diabetes* 44:369–374, 1995