Gender Difference in the Impact of Type 2 Diabetes on Coronary Heart Disease Risk

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OBJECTIVE — To explain the stronger effect of type 2 diabetes on the risk of coronary heart disease (CHD) in women compared with men.

RESEARCH DESIGN AND METHODS — The study population consisted of 1,296 nondiabetic subjects and 835 type 2 diabetic subjects aged 45–64 years without cardiovascular disease. The end points were CHD death and a major CHD event (CHD death or nonfatal myocardial infarction). The follow-up time was 13 years.

RESULTS — Major CHD event rate per 1,000 person-years was 11.6 in nondiabetic men, 1.8 in nondiabetic women, 36.3 in diabetic men, and 31.6 in diabetic women. The diabetes-related hazard ratio for a major CHD event from the Cox model, adjusted for age and area of residence, was 2.9 (95% CI 2.2–3.9) in men and 14.4 (8.4–24.5) in women, and after further adjustment for cardiovascular risk factors, 2.8 (2.0–3.7) and 9.5 (5.5–16.9), respectively. The burden of conventional risk factors in the presence of diabetes was greater in women than in men at baseline. Prospectively, elevated blood pressure, low HDL cholesterol, and high triglycerides contributed to diabetes-related CHD risk more in women than in men. However, after adjusting for conventional risk factors, a substantial proportion of diabetes-related CHD risk remained unexplained in both genders.

CONCLUSIONS — The stronger effect of type 2 diabetes on the risk of CHD in women compared with men was in part explained by a heavier risk factor burden and a greater effect of blood pressure and atherogenic dyslipidemia in diabetic women.

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Type 2 diabetes increases the risk of coronary heart disease (CHD) more markedly in women than in men. However, the reported magnitudes of the diabetes-related CHD risk in men and women vary widely between different studies (1–5). The greater relative risk of CHD in diabetic women still remains incompletely understood, but several explanations can be offered. First, adverse changes induced by type 2 diabetes in some cardiovascular risk factors, such as HDL cholesterol, triglycerides, LDL particle size, and blood pressure, have been found to be more pronounced in women than in men (6–8). Second, it is possible that gender may alter the effect of some cardiovascular risk factors for CHD in diabetic subjects, leading to a stronger risk effect in women. Third, diabetes in women may interfere more with protective mechanisms in the vascular wall and thereby lead to enhanced atherogenesis and/or thrombogenesis (9).

In the present study, based on 13 years of follow-up of 1,296 nondiabetic and 835 type 2 diabetic subjects, we evaluated possible explanations for the stronger effect of type 2 diabetes on the risk of CHD in women than in men.

RESEARCH DESIGN AND METHODS

Altogether, 1,059 subjects (581 men and 478 women) with type 2 diabetes aged 45–64 years and born and living in the Turku University Hospital district in West Finland and in the Kuopio University Hospital district in East Finland were identified through a national drug reimbursement register. A random sample of nondiabetic subjects aged 45–64 years from the same area was taken from the population register. The final sample comprised 1,373 nondiabetic subjects (638 men and 735 women).

The baseline examination conducted in 1982–1984 has been previously described in detail (10). Hospital records of those participants who reported that they had been hospitalized for cardiovascular disease were reviewed. Modified World Health Organization (WHO) criteria for definite or possible myocardial infarction (MI), based on chest pain symptoms, electrocardiogram changes, and cardiac enzymes, were used to verify the diagnosis of previous MI (11). The diagnosis of a previous stroke was based on the WHO criteria: a neurological deficit observed by a physician and persisting for >24 h, without other disease explaining the symptoms (12). Nontraumatic lower-extremity amputations were recorded.

The present study population consisted of 583 nondiabetic men (283 from East Finland and 300 from West Finland) and 713 nondiabetic women (323 and 390, respectively) and 429 men (172 and 257, respectively) and 406 women (212 and 194, respectively) with type 2 diabetes, who were free of clinically significant atherosclerotic cardiovascular disease (verified previous MI, stroke, or nontraumatic lower-extremity amputations) at

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Abbreviations: CHD, coronary heart disease; MI, myocardial infarction; WHO, World Health Organization.

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

baseline. Baseline characteristics according to gender are shown in Table 1.

The follow-up period lasted until 1 January 1996. Copies of death certificates of deceased participants were obtained from the Cause-of-Death Register (Statistics Finland). In the final classification of causes of death, hospital and autopsy records, if available, were also used. Information about hospitalizations for cardiovascular disease was obtained from answers to a postal questionnaire sent to surviving participants and from the computerized National Hospital Discharge Register. Hospital records of those participants who had been hospitalized for a chest pain attack were reviewed by one of the investigators, and the diagnosis of MI was ascertained similarly to the baseline study. The two end points used in this study were CHD death and a major CHD event (CHD death or nonfatal MI).

The Ethics Committees of the Kuopio University Hospital and the Turku University Central Hospital approved the study. All study subjects gave informed consent.

Statistical analysis

Data analyses were conducted with the SPSS 11.5.1 programs (SPSS, Chicago, IL). The results for continuous variables are given as means ± SD, and those for categorical variables are given as percentages. The group differences in continuous variables were evaluated by univariate ANOVAs with adjustment for age and area of residence. Logarithmic transformation was used for triglycerides. Two-way ANOVA for continuous variables and logistic regression analysis for dichotomous variables were carried out to evaluate the interaction between gender and diabetes for each risk factor, with adjustment for age and area of residence. The differences in the cumulative survival between the groups were studied by Kaplan-Meier estimates, with log-rank test statistics. Multivariate Cox regression models were used to examine the association of cardiovascular risk factors with the end points and interactions of cardiovascular risk factors with gender. Trends over the risk factor tertiles were investigated with the χ^2 test for trend.

RESULTS

Effect of gender on risk factor levels

At baseline, both nondiabetic and diabetic women, compared with their male

Table 1—*Baseline characteristics of nondiabetic and diabetic men and women*

	Nondiabetic		Diabetic		*P*-value (adjusted for age and area of residence)				
					Men vs. women		Diabetic vs. nondiabetic		Interaction for
	Men	Women	Men	Women	Nondiabetic	Diabetic	Men	Women	gender × diabetes
Subjects (*n*)	583	713	429	406	—	—	—	—	—
Age (years)	54.4 ± 5.6	54.8 ± 5.5	56.9 ± 5.1	58.7 ± 4.9	—	—	—	—	—
Current smokers (%)	30.7	9.8	25.4	7.4	<0.001	<0.001	0.248	0.927	0.971
BMI (kg/m^2)	26.0 ± 3.2	27.0 ± 4.6	28.1 ± 4.5	30.5 ± 5.9	<0.001	<0.001	<0.001	<0.001	0.001
Systolic blood pressure (mmHg)	138.0 ± 19.6	143.77 ± 21.3	147.2 ± 20.1	158.7 ± 25.2	<0.001	<0.001	<0.001	<0.001	0.057
Total cholesterol (mmol/l)	6.63 ± 1.25	6.95 ± 1.41	6.38 ± 1.40	6.99 ± 1.94	<0.001	<0.001	0.009	0.070	0.140
HDL cholesterol (mmol/l)	1.36 ± 0.36	1.62 ± 6.95	1.20 ± 0.35	1.28 ± 0.38	<0.001	0.007	<0.001	<0.001	<0.001
Triglycerides (mmol/l)	1.50 ± 0.78	1.32 ± 0.61	2.21 ± 2.10	2.78 ± 3.47	<0.001	<0.001	<0.001	<0.001	<0.001
Fasting glucose (mmol/l)	5.5 ± 0.7	5.3 ± 0.6	11.1 ± 3.8	12.3 ± 3.8	<0.001	<0.001	<0.001	<0.001	<0.001
HbA_1 (%)	—	—	9.7 ± 2.3	10.2 ± 2.2	—	0.001	—	—	—
Duration of diabetes (years)	—	—	8.0 ± 4.0	7.9 ± 3.9	—	0.305	—	—	—

Data are means ± SD unless otherwise indicated.

counterparts, smoked less frequently and had higher BMI, systolic blood pressure, total cholesterol, and HDL cholesterol (Table 1). Triglycerides were lower in nondiabetic women and higher in diabetic women compared with men. In a comparison of diabetic men and women with their nondiabetic counterparts, diabetic subjects of both genders had higher BMI, systolic blood pressure, and triglycerides and lower HDL cholesterol. Diabetic women had higher fasting glucose and HbA_1 than diabetic men. Significant gender $\times$ diabetes interactions, with more adverse effect of diabetes in women, were noted for BMI, triglycerides, and HDL cholesterol. For systolic blood pressure, the interaction was close to significance ($P = 0.057$).

Incidence of CHD death and a major CHD event

During the 13-year follow-up, the number of deaths from all causes/CHD deaths/first major CHD events was 102/37/79 in 583 nondiabetic men, 53/6/16 in 713 nondiabetic women, 214/101/151 in 429 diabetic men, and 195/90/126 in 406 diabetic women. The respective event-rates per 1,000 person-years were 14.4/5.2/11.6 in nondiabetic men, 5.9/0.7/1.8 in nondiabetic women, 47.7/22.5/36.3 in diabetic men, and 46.6/21.5/31.6 in diabetic women. Figure 1 shows Kaplan-Meier curves for cumulative incidence of CHD death and major CHD events by gender and diabetes status. Among nondiabetic subjects, there was a marked male excess in CHD mortality and incidence of major CHD events, whereas among diabetic subjects, the gap between men and women was almost abolished. The proportion of fatal events of all first CHD events was 47% in nondiabetic men, 38% in nondiabetic women, 67% in diabetic men, and 71% in diabetic women.

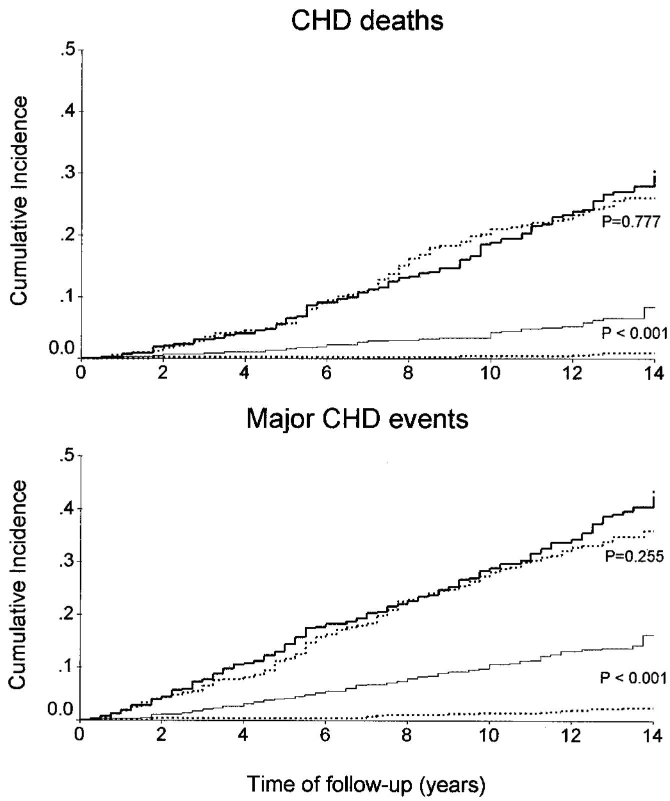

Figure 1—*Kaplan-Meier curves for cumulative incidence (proportion with event) of CHD mortality and major CHD events according to gender and diabetes status during 13 years of follow-up. The curves with small dashes indicate women: the lowest curve is for nondiabetic women, and the upper curve is for diabetic women. The lower continuous line denotes nondiabetic men, and the bold continuous line denotes diabetic men.* P *values denote log-rank test statistics for gender differences in nondiabetic and diabetic subjects.*

Influence of gender on the effect of risk factors

Among nondiabetic subjects, significant predictors of CHD risk (Table 2) were as follows: smoking for CHD death and major CHD events in men and women, BMI (low) for major CHD events in men, systolic blood pressure for CHD death in men and women and for major CHD events in men, total cholesterol for CHD death and major CHD events in men, HDL cholesterol for major CHD events in men and women, triglycerides for major CHD events in women, and fasting glucose (low) for CHD death in men. Significant gender $\times$ risk factor interactions in the prediction of major CHD events, with a stronger effect in women, were noted for BMI and triglycerides.

Among diabetic subjects, significant predictors of CHD risk were as follows: smoking for CHD death and major CHD events in men, BMI for CHD death, systolic blood pressure for CHD death and major CHD events in women, total cholesterol for CHD death and major CHD events in men, HDL cholesterol for CHD death and major CHD events in women, fasting glucose for CHD death and major CHD events in men and women, and HbA_1 and duration of diabetes for CHD death and major CHD events in women. A significant gender $\times$ risk factor interaction in the prediction of CHD death and major CHD events was observed for systolic blood pressure, with a stronger effect in women, and for total cholesterol, with a stronger effect in men. A stronger effect of diabetes duration in the prediction of CHD death in women was close to significance ($P = 0.067$). Interaction between the diabetes duration and plasma fasting glucose was observed in women (in the age- and area-adjusted model, the P value for interaction term was 0.032 for CHD death and 0.051 for a major CHD event) but not in men.

Figure 2 illustrates the incidence of a major CHD event per 1,000 person-years over risk factor tertiles. The effect of BMI was not statistically significant over tertiles in any of the groups. Total cholesterol in men and systolic blood pressure in women had a significant effect on CHD events over tertiles, independently of the diabetes status. Low HDL cholesterol was associated with CHD events significantly in diabetic women and nondiabetic men. The risk increased significantly over triglyceride tertiles in all four groups. In diabetic men and women, the risk increased significantly and similarly over fasting glucose tertiles. The same applied to HbA_1 (data not shown).

Diabetes-related hazard ratio after adjustment for other risk factors

The diabetes-related hazard ratios (HRs) for CHD death and a major CHD event, adjusted for age and area of residence, were markedly higher in women than in men (Table 3). The adjustment for individual cardiovascular risk factors and their different combinations of risk factors more strongly influenced HRs in women than in men with a few exceptions (smoking and total cholesterol). The difference in χ^2 values from log-likelihood tests comparing model 9 with model 1, excluding and including diabetes, was markedly greater in women than in men. This indicates that a larger proportion of diabetes-related CHD risk was due to diabetes itself in women. In Cox model analyses combining data on nondiabetic and diabetic men and women and including, in addition to risk factors of model 9, diabetes status and gender × diabetes as variables, the interaction term was highly significant, also indicating a stronger effect of diabetes on the risk in women than in men ($P < 0.001$ in CHD death model, $P < 0.001$ in major CHD event model).

CONCLUSIONS — Our study showed a considerably higher diabetes-related relative risk for a major CHD event in diabetic women (HR 14.7) than in men (HR 3.8). In terms of absolute risk of CHD death or a major CHD event, diabetes almost completely abolished the female protection from CHD. We found that the burden of obesity, elevated blood pressure, and atherogenic dyslipidemia (low HDL cholesterol and high triglycerides) was, in the presence of diabetes, greater in women than in men already at baseline. We also found that, during the follow-up, elevated blood pressure and atherogenic dyslipidemia contributed more strongly to diabetes-related CHD risk in women than in men. However, after adjusting for conventional risk factors, a substantial proportion of diabetes-related CHD risk remained unexplained in both genders. Poor glycemic control was an important predictor of CHD risk in both diabetic men and women.

The small number of CHD deaths in nondiabetic women is an important limitation of our study. However, our results

Table 2 —*HRs of CHD death and a major CHD event and 95% CIs in Cox multivariate models for nondiabetic and diabetic subjects according to gender*

	Nondiabetic							Diabetic						
	Men			Women			*P* for interaction with gender	Men			Women			*P* for interaction with gender
	HR	95% CI	*P*	HR	95% CI	*P*		HR	95% CI	*P*	HR	95% CI	*P*	
CHD death														
Current smoking (no, yes)	3.32	1.70–6.47	<0.001	8.78	1.49–51.8	<0.001	—	1.57	1.01–2.44	0.043	0.75	0.23–2.45	—	—
BMI (kg/m^2)	0.98	0.88–1.09	—	1.10	0.92–1.31	—	—	1.05	1.00–1.09	0.032	1.01	0.97–1.05	—	—
Systolic blood pressure (10 mmHg)	1.22	1.06–1.39	0.005	1.44	1.02–2.02	0.036	—	0.94	0.84–1.05	—	1.13	1.04–1.22	0.003	0.003
Total cholesterol (mmol/l)	1.35	1.06–1.72	0.014	1.05	0.58–1.88	—	—	1.21	1.08–1.36	0.001	1.03	0.92–1.16	—	0.040
HDL cholesterol (mmol/l)	0.74	0.28–1.91	—	0.60	0.05–7.36	—	—	0.79	0.43–1.44	—	0.40	0.20–0.82	0.011	—
Triglycerides (mmol/l)*	0.95	0.59–1.52	—	2.08	0.77–5.62	—	—	0.95	0.88–1.04	—	1.07	1.00–1.14	0.082	—
Fasting glucose (mmol/l)	0.54	0.31–0.95	0.033	0.44	0.11–1.75	—	—	1.12	1.07–1.19	<0.001	1.10	1.04–1.16	0.001	—
HbA_1 (%)	—	—	—	—	—	—	—	1.03	0.97–1.10	—	1.09	1.03–1.15	0.002	—
Duration of diabetes (years)	—	—	—	—	—	—	—	1.02	0.96–1.08	—	1.08	1.02–1.14	0.008	0.067
Major CHD event														
Current smoking (no, yes)	2.75	1.74–4.34	<0.001	7.57	2.48–23.1	<0.001	—	1.47	1.02–2.13	0.037	1.47	0.70–3.10	—	—
BMI (kg/m^2)	0.92	0.85–0.99	0.023	1.07	0.95–1.19	—	0.043	1.02	0.98–1.06	—	0.99	0.96–1.03	—	—
Systolic blood pressure (10 mmHg)	1.23	1.11–1.38	<0.001	1.16	0.93–1.44	—	—	0.99	0.91–1.08	—	1.14	1.06–1.22	<0.001	0.011
Total cholesterol (mmol/l)	1.36	1.16–1.59	<0.001	1.22	0.87–1.71	—	—	1.16	1.05–1.28	0.005	1.04	0.94–1.14	—	—
HDL cholesterol (mmol/l)	0.29	0.14–0.62	0.001	0.26	0.05–1.21	0.086	—	0.69	0.42–1.14	—	0.48	0.27–0.84	0.010	—
Triglycerides (mmol/l)*	1.15	0.88–1.49	—	2.53	1.50–4.29	0.004	0.020	0.96	0.87–1.05	—	1.08	1.00–1.17	—	—
Fasting glucose (mmol/l)	0.80	0.55–1.15	—	0.76	0.33–1.74	—	—	1.08	1.03–1.12	0.001	1.09	1.04–1.14	0.001	—
HbA_1 (%)	—	—	—	—	—	—	—	1.05	0.98–1.13	—	1.09	1.03–1.15	0.002	—
Duration of diabetes (years)	—	—	—	—	—	—	—	1.03	0.98–1.07	—	1.07	1.02–1.12	0.009	—

*HR (95% CI) is calculated using nontransformed values, but statistical significance is calculated using log-transformed values. The models are adjusted for age and area of residence, and variables enforced into the models are current smoking, BMI, systolic blood pressure, total cholesterol, HDL cholesterol, fasting glucose, and, additionally in type 2 diabetic subjects, duration of diabetes. Triglycerides (with HDL cholesterol omitted) and HbA_1 (with fasting glucose omitted) are similarly tested in the multivariate models. *P* values are shown only if they are <0.10.

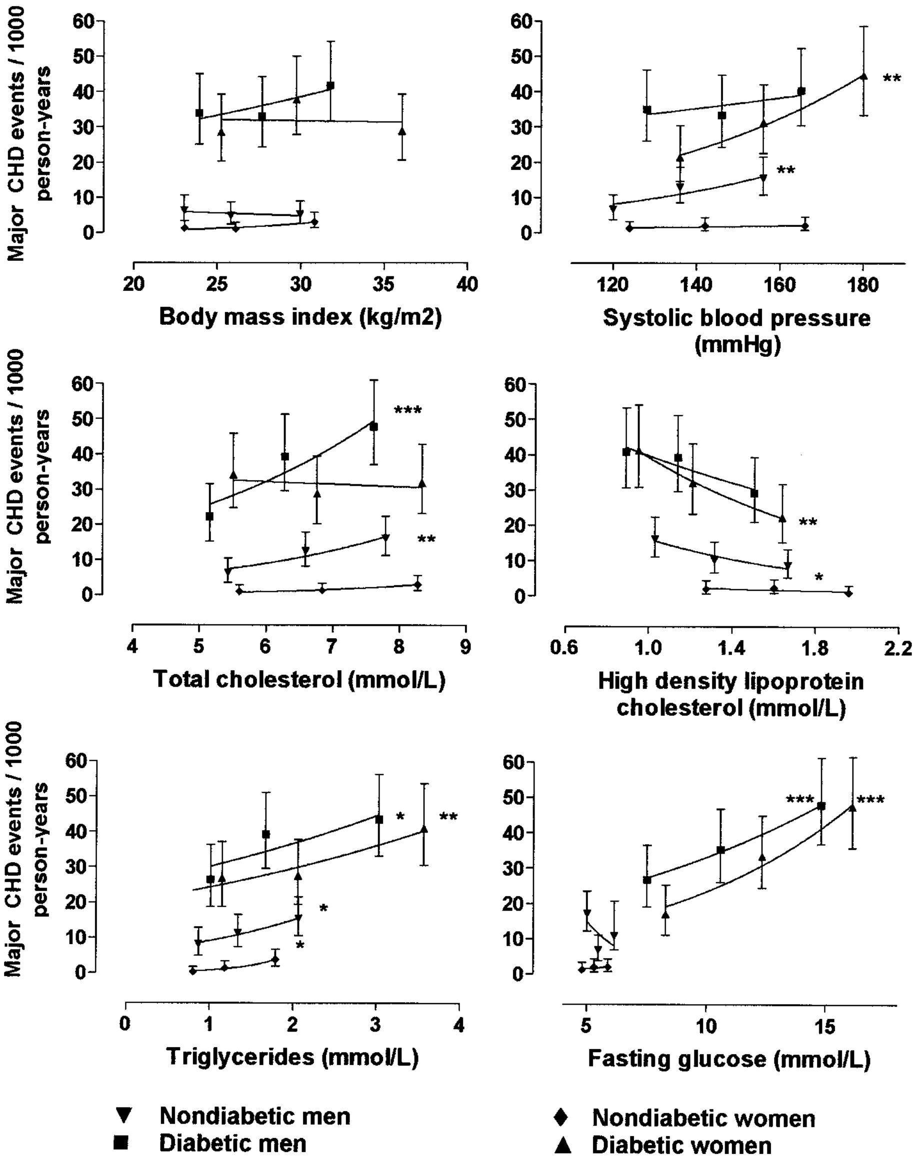

Figure 2—*Event rates for major CHD per 1,000 person-years according to tertiles of risk factors in nondiabetic and diabetic men and women. Event rates and their 95% CIs are plotted by median values of the diabetes status- and gender-specific tertiles of risk factors in nondiabetic men, nondiabetic women, diabetic men, and diabetic women.* χ^2 *test for trend:* *P < *0.05:* **P < *0.01:* ***P < *0.001.*

based on CHD mortality were consistent with those based on major CHD events.

The mechanisms leading to a greater augmentation of CHD risk of diabetic women compared with that of diabetic men have remained largely unknown. In our study, diabetic women had a particularly marked clustering of adverse changes in cardiovascular risk factors. Gender differences with more adverse effects of diabetes on the lipid profile (low HDL cholesterol and apolipoprotein A1 levels, increased levels of LDL cholesterol, small and dense LDL, apolipoprotein B, and triglycerides) and blood pressure in women compared with men have been reported (6–8). Diabetes may also alter estrogen-related protective mechanisms (9). Furthermore, low-grade inflammation may have a greater role in perturbing insulin action in women, or inflammatory factors may interact with female sex hormones, resulting in a decrease of protective effects of estrogens on body fat distribution and insulin action (13).

Poor glycemic control has been consistently associated with cardiovascular disease in patients with type 2 diabetes (14–23). We also found that poor glycemic control combined with a long duration of the disease increased the risk for CHD, particularly in diabetic women. Furthermore, elevated blood pressure and atherogenic dyslipidemia predicted CHD events, particularly in diabetic women. When we compared our results of this 13-year follow-up to the 7-year follow-up data of the same cohort (20), the role of glycemic control was now more pronounced, suggesting that glycemic control may become a more important predictor of CVD events along with a longer follow-up. Therefore, it is possible that trials aiming at improvement of glycemic control (24) may have underestimated the true effect of hyperglycemia on the risk of CHD. Successful strategy to reduce the burden of CHD in diabetic subjects is not only to normalize elevated blood pressure and atherogenic dyslipidemia, but also to improve glycemic control.

Type 2 diabetes–related CHD risk in women was to a greater extent explained by cardiovascular risk factors associated with insulin resistance (obesity, elevated blood pressure, low HDL cholesterol, high triglycerides) compared with men.

The greater relative diabetes-related CHD risk in women requires early intervention, particularly because the clustering of cardiovascular risk factors is more pronounced among women than among men already in the pre-diabetic state (25). Recent findings from the Steno-2 Study (26) show that multifactorial risk factor intervention substantially reduced the risk of cardiovascular disease in patients with type 2 diabetes. These preventive measures should be particularly intensive in diabetic women.

Table 3—HR (95% CI) and χ^2 difference, including significance, in different multivariate Cox models for diabetes-related risk of CHD death and a major CHD event in men and women

	Men		Women		Men		Women	
	CHD death (138 of 1,012)*	Major CHD event (230 of 1,012)	CHD death (96 of 1,119)	Major CHD event (142 of 1,119)	CHD death	Major CHD event	CHD death	Major CHD event
Model 1: Age and area	4.03 (2.74–5.91)	2.92 (2.21–3.86)	23.83 (10.33–54.99)	14.37 (8.43–24.47)	—	—	—	—
Model 2: 1 + smoking	4.15 (2.83–6.09)	2.99 (2.27–3.95)	23.84 (10.33–55.02)	14.35 (8.43–24.43)	−3.1 (NS)	−2.9 (NS)	0.0 (NS)	0.1 (NS)
Model 3: 1 + BMI	3.73 (2.52–5.52)	2.86 (2.15–3.80)	23.10 (9.93–53.73)	14.35 (8.35–24.67)	8.9 (0.003)	4.9 (0.027)	10.3 (0.001)	10.8 (0.001)
Model 4: 1 + sBP	3.96 (2.68–5.85)	2.82 (2.12–3.74)	20.73 (8.94–48.06)	12.63 (7.34–21.61)	3.3 (NS)	6.1 (0.014)	18.1 (<0.001)	23.1 (<0.001)
Model 5: 1 + total cholesterol	4.22 (2.88–6.19)	3.03 (2.30–4.00)	24.16 (10.48–55.74)	14.57 (8.56–24.80)	−4.8 (0.028)	−4.6 (0.032)	−0.9 (NS)	−2.0 (NS)
Model 6: 1 + HDL cholesterol	3.84 (2.60–5.67)	2.70 (2.03–3.58)	16.86 (7.14–39.84)	10.49 (6.01–18.30)	5.8 (0.016)	10.9 (0.001)	45.8 (<0.001)	60.6 (<0.001)
Model 7: 1 + logTG	3.46 (2.34–5.13)	2.59 (1.95–3.45)	18.00 (7.66–42.32)	10.86 (6.24–18.89)	15.0 (<0.001)	16.0 (<0.001)	40.0 (<0.001)	56.5 (<0.001)
Model 8: 1 + BMI + sBP + HDL cholesterol + logTG	3.40 (2.28–5.08)	2.50 (1.87–3.35)	14.47 (6.06–34.56)	9.31 (5.28–16.43)	18.6 (<0.001)	21.3 (<0.001)	60.7 (<0.001)	78.8 (<0.001)
Model 9: 1 + smoking + BMI + sBP + total cholesterol + HDL cholesterol + logTG	3.77 (2.52–5.65)	2.75 (2.05–3.70)	14.74 (6.16–35.27)	9.54 (5.39–16.87)	12.3 (<0.001)	13.6 (<0.001)	61.1 (<0.001)	79.0 (<0.001)

Data are HRs (95% CI) or difference in χ^2 values from log-likelihood test comparisons with model 1, excluding and including diabetes (corresponding P value). *Number of events per number of subjects. logTG, log-transformed triglycerides; sBP, systolic blood pressure.

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