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The Gender-Specific Impact of Diabetes and Myocardial Infarction at Baseline and During Follow-Up on Mortality From All Causes and Coronary Heart Disease

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OBJECTIVES The goal of this study is to compare the magnitude of diabetes and myocardial infarction (MI) at baseline and during follow-up on cause-specific and all-cause mortality.

BACKGROUND History of both MI and diabetes are strong predictors of coronary heart disease (CHD) death. However, gender-specific data on the joint effect of diabetes and MI, and particularly on the effect of incident diabetes and MI developed during the follow-up, on CHD mortality are scarce.

METHODS The baseline cohort study included 2,416 patients with prior diabetes or MI at baseline; the follow-up cohort study included 4,315 patients with incident diabetes or MI diagnosed during the follow-up.

RESULTS In the baseline cohort study, men with prior MI had a 20% to 80% increased risk of CHD or total mortality, but women with prior MI had a 43% to 45% decreased risk of CHD or total mortality in comparison with men and women with prior diabetes. In the follow-up cohort study, men and women with incident MI had a higher risk of CHD mortality (hazard ratio [HR] 2.15 in men and 1.65 in women), and an almost similar risk of total mortality (HR 0.95 in men and 1.02 in women) in comparison with men and women with incident diabetes.

CONCLUSIONS In men, MI at baseline or during follow-up confers a greater risk on CHD mortality than diabetes does. In women, prior MI at baseline confers a lower risk on CHD mortality than prior diabetes does, but incident MI during follow-up confers a greater risk than incident diabetes does. In both men and women, total mortality is similar for incident MI and diabetes. (J Am Coll Cardiol 2005;45:1413–8) © 2005 by the American College of Cardiology Foundation

The number of diabetic patients in the world has been estimated to at least double during the next 30 years (1). Cardiovascular disease (CVD) accounts for more than 75% of total mortality among patients with type 2 diabetes (2). Epidemiological studies have indicated that patients with type 2 diabetes have a two to four times greater risk of CVD mortality than those without diabetes. In recent years, several studies compared the magnitude of the risk of history of type 2 diabetes and myocardial infarction (MI) on subsequent coronary heart disease (CHD) or CVD mortality (3–10). A Finnish prospective study found that the risk of CHD death among diabetic subjects without prior MI was similar to nondiabetic subjects with prior MI (3), but this finding has been challenged by several later studies (5–10). These observational studies usually have a single baseline measurement (3–10). Only one study has presented the data on the exposure status changes during the follow-up, but it adjusted for age only, not taking into account other CVD risk factors (6). Thus far no study has compared the impact of diabetes and MI at baseline and during follow-up on CHD mortality with adjustment for major CVD risk factors. The aim of this study is to compare the independent and joint effects of diabetes and MI at baseline and during follow-up on CHD, CVD, non-CVD, and total mortality.

METHODS

Subjects. Six independent population surveys were carried out in five geographic areas of Finland in 1972, 1977, 1982, 1987, 1992, and 1997 (11). In 1972 and 1977, a randomly selected sample making up 6.6% of the population born between 1913 and 1947 was drawn. Since 1982, the sample was stratified by area, gender, and 10-year age group according to the World Health Organization MONICA (MONItoring trends and determinants of CArdiovascular disease) protocol (12). In six surveys, the subjects included were 25 to 64 years of age, and, in the 1997 survey, subjects age 65 to 74 years were also included. Subjects who participated in more than one survey were included in the first survey cohort only. The total sample size of the six surveys was 53,166. The participation rate varied by year from 74% to 88% (11). We carried out two studies in the present analyses: the baseline cohort study included patients with prior diabetes or MI at baseline (n = 2,416), and the follow-up cohort study included patients with incident (diagnosed after the baseline survey) diabetes or MI during follow-up (n = 4,315). These surveys were conducted

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Abbreviations and Acronyms

BMI = body mass index
CHD = coronary heart disease
CI = confidence interval
CVD = cardiovascular disease
HR = hazard ratio
ICD = International Classification of Diseases
MI = myocardial infarction

according to the ethical rules of the National Public Health Institute, and the investigations were carried out in accordance with the Declaration of Helsinki.

Measurements. A self-administered questionnaire was mailed to the participants. It included questions about smoking and medical history. Based on the responses, the participants were classified as never, previous, and current smokers. At the study site, specially trained research nurses measured blood pressure, height, and weight using a standardized protocol (12). Blood pressure was measured after 5 min of rest using a standard mercury manometer. Height was measured without shoes. Weight was measured with light clothing. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. After blood pressure measurement, a venous blood specimen was drawn. Total cholesterol concentration was determined by using the Lieberman Burchard method in 1972 and 1977, and an enzymatic method (CHOD-PAP, Boehringer Mannheim, Mannheim, Germany) since 1982. Because the enzymatic method gave 2.4% lower values than the Lieberman Burchard method, 1972 and 1977 values are corrected by this percentage. All samples were analyzed in the same laboratory at the National Public Health Institute.

Assessment of diabetes and MI at baseline and during follow-up. Assessment of diabetes and MI status was based on self-reporting and on the data of two nationwide registers. The National Hospital Discharge Register data included hospital discharge diagnosis from 1968 through the end of 2000. Validity of the data has been assessed and found to be generally good (13). Data on diabetes medication were ascertained from the National Social Insurance Institution's Register on special reimbursement for antidiabetic drugs from 1964 through the end of 2000. Antidiabetic drugs prescribed by a physician are free of charge in Finland and are subject to approval of a physician who reviews each case history. The physician confirms the diagnosis of diabetes by applying the World Health Organization criteria (14,15). All patients receiving free medication (either oral antidiabetic agents or insulin) are entered into a register maintained by the Social Insurance Institution.

Subjects who reported having diabetes on the questionnaire, or who had had a hospital discharge diagnosis of diabetes, or the approval for free-of-charge medication for diabetes before the baseline survey, were classified as having prior diabetes at baseline. The subjects with prior MI at baseline were those who reported having MI on the questionnaire, or had had a hospital discharge diagnosis of MI before the baseline survey.

Subjects who had the first hospital discharge diagnosis with diabetes, or the approval for free-of-charge medication for diabetes after the baseline survey were classified as having incident diabetes during the follow-up. Subjects with incident MI during the follow-up comprised those who had a hospital discharge with a diagnosis of MI after the baseline survey. Age and person-years of follow-up were calculated at their date of new diagnosis of diabetes or MI during follow-up. The patients who died within 28 days from the diagnosis date of incident diabetes and MI during follow-up were excluded from the analysis, thus eliminating the deaths directly due to MI.

Prospective follow-up. The study cohorts were followed until the end of 2001 through computerized register linkage using the personal identification number assigned for every resident in Finland. Mortality data were obtained from Statistics Finland. The International Classification of Diseases (ICD), Eighth, Ninth, and Tenth Revisions, were used for coding the causes of death; ICD codes 390-459 and I00-I99 were classified as CVD deaths, 410-414 and I20-I25 as CHD deaths.

Statistics. SPSS for Windows 11.5 was used for statistical analysis. The gender-specific CHD, CVD, non-CVD, and total mortality rates were calculated by 10-year age intervals and standardized for age by the direct method using a European standard population age 25 to 74 years (16) for each of three groups: diabetes, MI, and both. The Cox proportional hazard models (17) were used to estimate the hazard ratios (HRs) of cause-specific and all-cause mortality associated with diabetes and MI status. The reference group was the subjects with diabetes at baseline or during follow-up. The analyses were first carried out adjusting for age and study year only, and then adjusting further for BMI, systolic blood pressure, total cholesterol, and smoking at baseline. The likelihood ratio test for interaction was carried out to test whether the effect of disease status on mortality was the same in men and women. A p value of <0.05 was considered to be statistically significant, and all p values were two-sided.

RESULTS

Baseline cohort study. Baseline characteristics and multivariate-adjusted (age, study year, BMI, systolic blood pressure, cholesterol, and smoking) HRs of mortality according to the prior history of diabetes and MI at baseline are presented in Table 1. During a mean follow-up period of 12 years, we identified 1,119 deaths from all causes among 2,416 patients with prior diabetes and MI at baseline, of which 591 deaths were coded as CHD, 781 deaths as CVD, and 338 deaths as non-CVD. Compared with men with prior diabetes at baseline, men with prior MI had a higher risk of death from CHD (HR, 1.78; 95% confidence interval [CI], 1.39 to 2.27), from CVD (HR, 1.43; 95% CI, 1.16 to 1.77), and from all causes (HR, 1.22; 95% CI, 1.03

Table 1. Baseline Characteristics* and HR of Coronary Heart Disease, Cardiovascular, Noncardiovascular, and Total Mortality According to the History of Diabetes and MI at Baseline

	Men			Women		
	Prior Diabetes	Prior MI	Prior Diabetes and MI	Prior Diabetes	Prior MI	Prior Diabetes and MI
# of subjects	496	982	99	466	326	47
Age at baseline (yrs)	53.0	56.9	58.7	52.4	58.3	60.1
Body mass index (kg/m^2)	28.2	27.7	29.3	29.7	29.5	31.1
Diastolic blood pressure (mm Hg)	90	89	85	88	90	90
Systolic blood pressure (mm Hg)	151	147	150	152	153	161
Serum cholesterol (mmol/l)	6.1	6.5	6.3	6.3	6.8	6.7
Smoking (%)						
Never	31.5	16.8	19.2	79.2	78.5	78.7
Past	33.7	43.6	48.5	7.3	10.4	8.5
Current	34.9	39.6	32.3	13.5	11.1	12.8
Person-yrs	6,070	10,529	859	6,376	4,731	479
Coronary heart disease mortality						
# of deaths	85	320	42	74	53	17
Mortality rate/10,000 person-yrs†	117.3	208.5	365.9	88.7	55.6	226.3
Age and study year adjustment HR (95% CI)	1.00	1.87 (1.47–2.38)	2.93 (2.01–4.26)	1.00	0.58 (0.40–0.83)	2.73 (1.58–4.71)
Multivariate adjustment HR (95% CI)‡	1.00	1.78 (1.39–2.27)	2.97 (2.03–4.34)	1.00	0.57 (0.39–0.82)	2.26 (1.29–3.97)
Cardiovascular mortality						
# of deaths	127	371	56	120	86	21
Mortality rate/10,000 person-yrs†	173.6	244.4	503.0	148.8	110.4	272.8
Age and study year adjustment HR (95% CI)	1.00	1.46 (1.19–1.79)	2.65 (1.92–3.65)	1.00	0.61 (0.46–0.81)	2.09 (1.30–3.36)
Multivariate adjustment HR (95% CI)‡	1.00	1.43 (1.16–1.77)	2.76 (2.00–3.81)	1.00	0.63 (0.47–0.84)	1.84 (1.13–3.00)
Noncardiovascular mortality						
# of deaths	80	139	11	72	31	5
Mortality rate/10,000 person-yrs†	127.4	88.1	95.9	93.0	43.2	58.1
Age and study year adjustment HR (95% CI)	1.00	0.88 (0.66–1.16)	0.86 (0.46–1.63)	1.00	0.40 (0.26–0.62)	0.78 (0.31–1.97)
Multivariate adjustment HR (95% CI)‡	1.00	0.88 (0.66–1.17)	0.95 (0.50–1.80)	1.00	0.40 (0.26–0.62)	0.70 (0.28–1.78)
Total mortality						
# of deaths	207	510	67	192	117	26
Mortality rate/10,000 person-yrs†	301.0	332.4	598.9	241.8	153.6	330.9
Age and study year adjustment HR (95% CI)	1.00	1.24 (1.05–1.46)	1.97 (1.49–2.61)	1.00	0.54 (0.42–0.68)	1.58 (1.04–2.40)
Multivariate adjustment HR (95% CI)‡	1.00	1.22 (1.03–1.44)	2.08 (1.57–2.76)	1.00	0.55 (0.43–0.70)	1.41 (0.92–2.16)

*Baseline characteristics represent mean or percentage; †age-standardized mortality rate was calculated using a European standard population by 10-year age intervals; ‡adjusted for age at baseline, study year, body mass index, systolic blood pressure, total cholesterol, and smoking.
CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.

to 1.44). In women, however, those with prior MI had a lower risk of death from CHD (HR, 0.57; 95% CI, 0.39 to 0.82), from CVD (HR, 0.63; 95% CI, 0.47 to 0.84), from non-CVD (HR, 0.40; 95% CI, 0.26 to 0.62), and from all causes (HR, 0.55; 95% CI, 0.43 to 0.70) compared with women with prior diabetes at baseline. These gender differences in HRs were statistically significant for CHD mortality (chi-square = 23.58, 1 df, $p < 0.001$), CVD mortality (chi-square = 21.21, 1 df, $p < 0.001$), non-CVD mortality (chi-square = 8.24, 1 df, $p < 0.005$), and total mortality (chi-square = 29.5, 1 df, $p < 0.001$). Men and women with both prior diabetes and MI at baseline showed the highest risks of death from CHD, CVD, and all causes.

Patients with incident diabetes and MI during follow-up. For this cohort with a mean follow-up period of 7.7 years, we identified 1,578 deaths from all causes among 4,315 patients with incident diabetes or MI, of which 825 deaths were coded as CHD, 1,094 deaths as CVD, and 484 deaths as non-CVD (Table 2). Compared with men and women with incident diabetes, men and women with incident MI had higher multivariate-adjusted HRs of CHD mortality (2.15; 95% CI, 1.70 to 2.73 in men; 1.65; 95% CI, 1.27 to 2.14 in women) and CVD mortality (1.41; 95% CI, 1.16 to 1.71 in men; 1.22; 95% CI, 0.98 to 1.53 in women), lower HRs of non-CVD mortality (0.42; 95% CI, 0.33 to 0.55 in men; 0.66; 95% CI, 0.46 to 0.93 in women), and almost similar HRs of total mortality (0.95; 95% CI, 0.82 to 1.11 in men; 1.02; 95% CI, 0.84 to 1.23 in women). There was no gender difference in CHD, CVD, non-CVD, and all-cause mortality (chi-square = 1.30, 0.59, 2.32, and 0.23, respectively, 1 df, all $p > 0.1$). Men and women with both incident diabetes and MI showed the highest risks of CHD and total mortality.

The cumulative survival probability curves further illustrate the different patterns in CHD mortality associated with diabetes and MI status at baseline and during the follow-up (Fig. 1). Men with prior MI at baseline had a worse survival than men with prior diabetes did. However, the survival curves were reversed in women with prior diabetes at baseline being associated with a worse survival than was prior MI. When the disease status during follow-up was considered, men and women with incident MI had a worse survival in comparison with subjects with incident diabetes.

Table 2. Baseline Characteristics* and HR of Coronary Heart Disease, Cardiovascular, Noncardiovascular, and Total Mortality According to Incident Diabetes and MI During Follow-Up

	Men			Women		
	Incident Diabetes	Incident MI	Incident Diabetes and MI	Incident Diabetes	Incident MI	Incident Diabetes and MI
# of subjects	981	1,308	171	1,155	566	134
Age at diagnosed date (yrs)	60.1	59.5	58.6	64.2	66.1	63.3
Body mass index (kg/m^2)	29.2	26.5	29.3	31.0	27.5	31.7
Diastolic blood pressure (mm Hg)	94	92	96	94	92	97
Systolic blood pressure (mm Hg)	150	148	154	157	155	165
Serum cholesterol (mmol/l)	6.5	7.0	6.9	6.7	7.2	6.8
Smoking (%)						
Never	25.8	23.9	22.8	84.2	80.6	85.1
Past	26.9	22.3	28.7	3.0	3.4	2.2
Current	47.3	53.7	48.5	12.7	16.1	12.7
Person-yrs	6,607	11,215	971	9,304	4,646	662
Coronary heart disease mortality						
# of deaths	102	365	47	146	126	39
Mortality rate/10,000 person-yrs†	150.4	301.7	506.9	123.7	190.5	496.7
Age and study year adjustment HR (95% CI)	1.00	2.04 (1.64–2.55)	3.42 (2.42–4.84)	1.00	1.57 (1.23–1.99)	4.18 (2.92–5.98)
Multivariate adjustment HR (95% CI)‡	1.00	2.15 (1.70–2.73)	3.24 (2.28–4.60)	1.00	1.65 (1.27–2.14)	3.91 (2.73–5.60)
Cardiovascular mortality						
# of deaths	178	418	57	241	147	53
Mortality rate/10,000 person-yrs†	273.0	346.7	606.0	206.6	222.3	660.4
Age and study year adjustment HR (95% CI)	1.00	1.33 (1.11–1.59)	2.42 (1.79–3.27)	1.00	1.10 (0.90–1.36)	3.43 (2.53–4.63)
Multivariate adjustment HR (95% CI)‡	1.00	1.41 (1.16–1.71)	2.32 (1.71–3.14)	1.00	1.22 (0.98–1.53)	3.22 (2.38–4.36)
Noncardiovascular mortality						
# of deaths	143	126	22	131	49	13
Mortality rate/10,000 person-yrs†	226.2	111.5	205.2	119.3	105.1	185.3
Age and study year adjustment HR (95% CI)	1.00	0.49 (0.38–0.62)	1.22 (0.78–1.93)	1.00	0.65 (0.47–0.91)	1.57 (0.88–2.79)
Multivariate adjustment HR (95% CI)‡	1.00	0.42 (0.33–0.55)	1.30 (0.83–2.05)	1.00	0.66 (0.46–0.93)	1.61 (0.90–2.87)
Total mortality						
# of deaths	321	544	79	372	196	66
Mortality rate/10,000 person-yrs†	499.2	458.2	811.2	325.9	327.4	845.7
Age and study year adjustment HR (95% CI)	1.00	0.95 (0.83–1.10)	1.89 (1.48–2.42)	1.00	0.94 (0.79–1.12)	2.78 (2.13–3.62)
Multivariate adjustment HR (95% CI)‡	1.00	0.95 (0.82–1.11)	1.87 (1.46–2.40)	1.00	1.02 (0.84–1.23)	2.67 (2.05–3.48)

*Baseline characteristics represent mean or percentage; †age-standardized mortality rate was calculated using a European standard population by 10-year age intervals; ‡adjusted for age at diagnosed date, study year, body mass index, systolic blood pressure, total cholesterol, and smoking.
CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.

DISCUSSION

Men with prior history of MI at baseline were at higher risk of CHD and total mortality than men with history of diabetes at baseline; in women, the magnitude of the association was reversed, and prior diabetes at baseline was associated with a greater risk of CHD and total mortality than prior MI at baseline. When the disease status during follow-up was considered, men and women with incident MI had a higher risk of CHD mortality, and almost similar risk of total mortality in comparison with subjects with incident diabetes. Men and women with both diabetes and MI at baseline or during follow-up showed the highest risk.

Using the same design as our baseline cohort study, several previous studies compared the magnitude of the risk of history of type 2 diabetes and MI on subsequent CHD or CVD mortality (3–10), but the results were inconsistent. The analyses from another Finnish cohort study (3) and from the Nurses' Health study (4) found that the risk of CHD mortality among subjects with a history of diabetes without prior MI was similar to that in nondiabetic subjects with prior MI. The Health Professionals Follow-up study (5), a Scottish population-based study (6), the Atherosclerosis Risk in Communities study (9), and the Multiple Risk Factor Intervention trial (10) consistently reported that the magnitudes of CHD and CVD mortality were weaker for prior diabetes at baseline than that associated with prior MI. Only two studies compared CHD mortality associated with prior diabetes and established MI in men and women separately (7,8). In the Hoorn study, women with prior diabetes at baseline had a risk of CVD events that was similar to that of nondiabetic women with prior CVD, whereas nondiabetic men with prior CVD conferred a higher risk of CVD events compared with men with prior

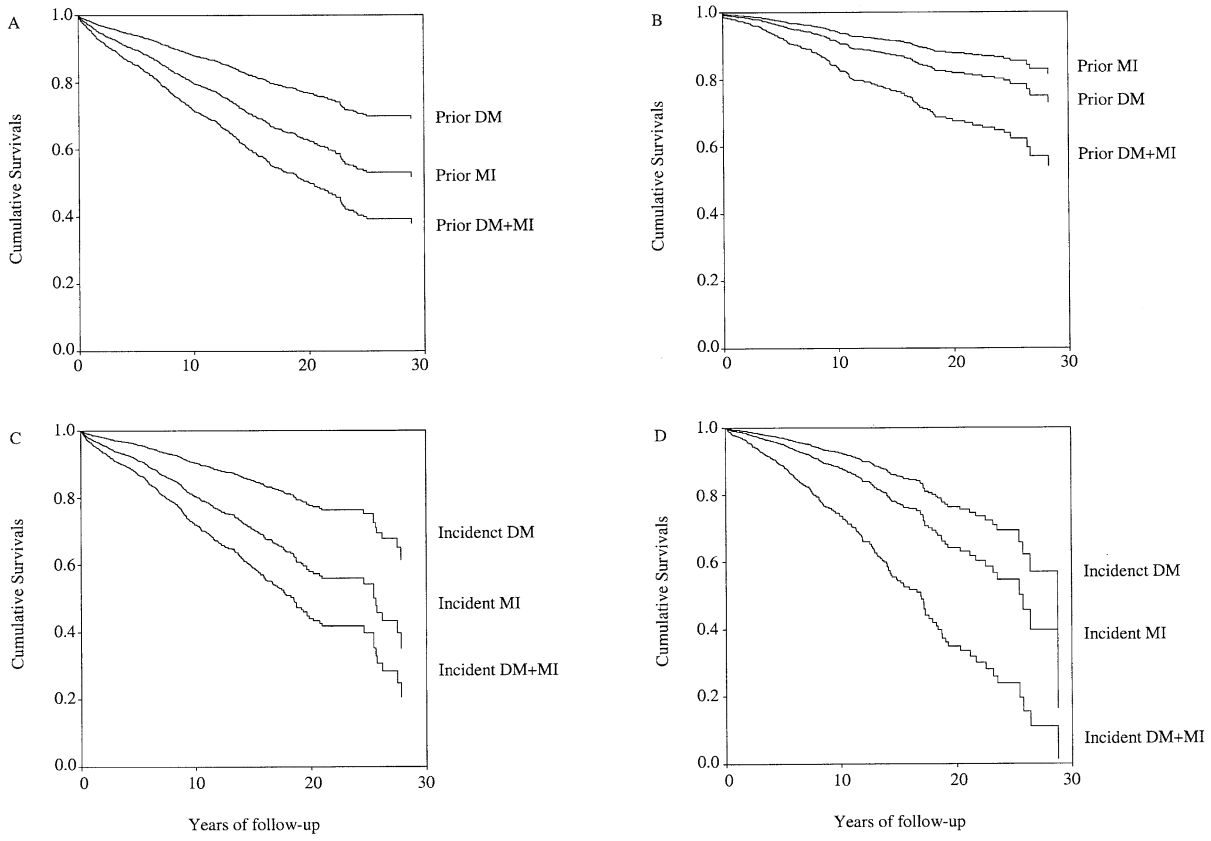

Figure 1. The multivariate-adjusted cumulative survival curves of coronary mortality associated with diabetes and myocardial infarction (MI) at baseline (**A** = men; **B** = women) and during follow-up (**C** = men; **D**= women). Adjusted for age, study year, body mass index, systolic blood pressure, total cholesterol, and smoking. DM = diabetes.

diabetes and without prior CVD (8). The analysis from the Framingham study indicated that, in men, prior CHD at baseline signifies a higher risk for CHD mortality than does prior diabetes; however, this was reversed in women, with prior diabetes being associated with greater risk for CHD mortality (7), which is consistent with our baseline cohort study.

Only data from a Scottish population-based study compared the magnitude of the incident diabetes and MI during the follow-up on the risk of CVD mortality (6), which used the same design as our follow-up cohort study. The present study showed a higher risk for CHD mortality, and almost similar risk for total mortality in patients with incident MI compared with patients with incident diabetes. The analysis from the Scottish population-based study found that patients with incident MI had a higher risk of CVD and total mortality than patients with incident diabetes had, but this study did not adjust for other CVD risk factors besides age and gender (6).

In the present study, women with prior MI at baseline had a markedly lower risk of CHD and total mortality compared with women with prior diabetes at baseline, whereas, in the follow-up study, this association was reversed, and women with incident MI had a higher risk compared with women with incident diabetes. The magnitude of the effect of diabetes and MI on CHD risk most probably depends on the duration of the disease, and this time factor may operate differently for diabetes than for MI. Among patients who have survived an acute MI, the risk of subsequent CHD event is highest right after the attack, and the risk stabilizes over time, whereas, among diabetic subjects, the risk increases with the duration of the disease (10). Most previous studies, similar to our baseline cohort analyses, have not paid attention to the time of the MI event, or the duration of diabetes, in their data analyses.

When comparing absolute mortality, the largest gender differential on CHD, CVD, and total mortality (adjusted for age) appeared in patients with MI and became smaller and almost nonexistent in diabetic patients. The findings from our study further support the hypothesis that the presence of diabetes reduces the usual female advantage regarding CHD (18,19). More aggressive management of diabetes to prevent CVD may be needed, particularly in women. The United Kingdom Prospective Diabetes study (UKPDS) demonstrated the importance of maintaining good glycemic control to prevent the development and progression of complications among patients with type 2 diabetes (20). Clinical trials have also shown that pharmacological treatment of hypertension (21–24) and cholesterol reduction with a statin therapy (25–27) are efficient ways to prevent CHD in diabetic patients. While a more efficient control of hyperglycemia and other CVD risk factors are important in all diabetic patients, it is possible that women

with diabetes may particularly benefit from more intensive intervention strategies to reduce the risk of CVD.

There are several strengths and limitations in our study. We have a unique possibility to stratify for both baseline and follow-up status of diabetes and MI. The number of patients is large and from a homogeneous population. The mean follow-up was sufficiently long, during which a large number of cardiovascular end point events were ascertained. We also excluded subjects with type 1 diabetes from the analysis. Finally, due to computerized data linkage of national mortality data, the end point data collection was practically complete. A limitation of our study was that we could not have the data on drug treatment for diabetes, MI, and other chronic diseases.

In conclusion, we compared the independent effects of diabetes and MI at baseline and during the follow-up on the risk of death. In men, MI at baseline or during the follow-up is associated with a greater risk on CHD mortality than seen with diabetes. In women, prior MI at baseline increases the risk of CHD mortality less than prior diabetes does, but incident MI during follow-up has a greater risk than incident diabetes. In both men and women, total mortality is similar between incident MI and diabetes during follow-up. The results of our study have important implications for clinical practice: first, we need to consider carefully the treatment strategies on individual disease status, particularly type 2 diabetes in women, for future CVD risk. Furthermore, in order to reduce CVD mortality, more active management and prevention of diabetes are needed.

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