

# The Impact of Diabetes Mellitus on Mortality From All Causes and Coronary Heart Disease in Women

## 20 Years of Follow-up

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**Background:** Few data are available on the long-term impact of type 2 diabetes mellitus on total mortality and fatal coronary heart disease (CHD) in women.

**Methods:** We examined prospectively the impact of type 2 diabetes and history of prior CHD on mortality from all causes and CHD among 121 046 women aged 30 to 55 years with type 2 diabetes in the Nurses' Health Study who were followed up for 20 years from 1976 to 1996.

**Results:** During 20 years of follow-up, we documented 8464 deaths from all causes, including 1239 fatal CHD events. Compared with women with no diabetes or CHD at baseline, age-adjusted relative risks (RRs) of overall mortality were 3.39 (95% confidence interval [CI], 3.08-3.73) for women with a history of diabetes and no CHD at baseline, 3.00 (95% CI, 2.50-3.60) for women with a history of CHD and no diabetes at baseline, and 6.84 (95% CI, 4.71-9.95) for women with both conditions at base-

line. The corresponding age-adjusted RRs of fatal CHD across these 4 groups were 1.0, 8.70, 10.6, and 25.8, respectively. Multivariate adjustment for body mass index and other coronary risk factors only modestly attenuated the RRs. Compared with nondiabetic persons, the multivariate RRs of fatal CHD across categories of diabetes duration ( $\leq 5$ , 6-10, 11-15, 16-25,  $> 25$  years) were 2.75, 3.63, 5.51, 6.38, and 11.9 ( $P < .001$  for trend), respectively. The combination of prior CHD and a long duration of clinical diabetes (ie,  $> 15$  years) was associated with a 30-fold (95% CI, 20.7-43.5) increased risk of fatal CHD.

**Conclusions:** Our data indicate that among women, history of diabetes is associated with dramatically increased risks of death from all causes and fatal CHD. The combination of diabetes and prior CHD identifies particularly high-risk women.

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**T**YPE 2 DIABETES mellitus is a well-established risk factor for coronary heart disease (CHD).<sup>1</sup> Diabetic women are at particularly high risk of CHD<sup>2</sup>; diabetes eliminates the usual female advantage for coronary disease mortality. Women with type 2 diabetes, compared with age-matched nondiabetic women, have a 5- to 7-fold higher rate of CHD death, with an event rate similar to that observed in men with type 2 diabetes.<sup>3</sup> Two recent analyses<sup>4,5</sup> have suggested that the magnitude of diabetes-related CHD mortality rivals the excess risk conferred by prior CHD. This finding challenges the National Cholesterol Education Program, which recommends more aggressive lipid-lowering therapy for people with prior CHD than for those with diabetes.<sup>6</sup> However, these studies were relatively small and did not consider duration of diabetes. Also, the results for diabetic men and women were combined, although it is known that diabetes

confers a particularly high risk of CHD in women.<sup>2</sup>

The present study, with 20 years of follow-up, examines the impact of type 2 diabetes on mortality from all causes and from CHD among women in the Nurses' Health Study. In particular, we compared the risk of fatal CHD and total mortality among diabetic women without clinical CHD with that of women diagnosed as having CHD but not diabetes. We also examined the impact of duration of clinical diabetes on CHD risk.

## RESULTS

During 20 years of follow-up from 1976 to 1996 (2341 338 person-years), we documented 8464 deaths from all causes, including 1239 cases of fatal CHD. A total of 1892 deaths were ascribed to cardiovascular disease and 6572 were attributed to other causes (mainly cancer). **Table 1** presents characteristics of the participants in the middle year (1986) of the follow-up.

## PARTICIPANTS AND METHODS

### STUDY POPULATION

The Nurses' Health Study cohort was established in 1976 when 121 700 female registered nurses, aged 30 to 55 years and residing in 11 large states, completed a mailed questionnaire about their medical history and lifestyle. Every 2 years, follow-up questionnaires have been sent to update information on potential risk factors and to identify newly diagnosed cases of CHD and other illness. After excluding the relatively few women ( $n=343$ ) whose diabetes was diagnosed at 30 years or younger (since they were most likely to have type 1 diabetes mellitus) and those with missing data on date of diagnosis of diabetes, the final population for analyses included 121 046 women.

### ASSESSMENT OF HISTORY OF CHD

At baseline and every 2 years during follow-up, we asked the women to report whether they had angina pectoris, coronary bypass surgery or angioplasty, and/or myocardial infarction (MI). In this study, only report of a prior MI was considered as history of CHD. In 1976, 394 women reported a history of MI. During the follow-up from 1976 to 1994, 2473 women reported newly diagnosed MI. The confirmation of self-reported MI through medical record review according to strict diagnostic criteria was approximately 68% before 1984.<sup>7</sup> This increased to 82% between 1990 and 1996 (unpublished data). Most of the nonconfirmed cases had coronary disease but did not meet the criteria for MI.

### CONFIRMATION OF DIABETES MELLITUS

In 1976, 1715 women reported physician-diagnosed diabetes (limited to diagnosis at age  $>30$  years). During the

follow-up periods, 6046 women reported newly diagnosed diabetes mellitus. A supplementary questionnaire regarding symptoms, diagnostic tests, and hypoglycemic therapy was mailed to women who indicated on any biennial questionnaire that they had been diagnosed as having diabetes. A case of diabetes was considered confirmed if at least 1 of the following was reported on the supplementary questionnaire: (1) 1 or more classic symptoms (excessive thirst, polyuria, weight loss, hunger, pruritus) plus fasting plasma glucose level of at least 140 mg/dL (7.8 mmol/L) or random plasma glucose level of at least 200 mg/dL (11.1 mmol/L); (2) at least 2 elevated plasma glucose concentrations on different occasions (fasting glucose level of at least 140 mg/dL or random plasma glucose level of at least 200 mg/dL and/or a concentration at least 200 mg/dL after 2 hours or more on oral glucose tolerance testing) in the absence of symptoms; or (3) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). The validity of this questionnaire has been verified in a subsample of this study population.<sup>8</sup> Among a random sample of 84 women classified by the questionnaire as having type 2 diabetes, 71 gave permission for their medical records to be reviewed and records were available for 62. An endocrinologist (J.E.M.), blinded to the information reported on the supplementary questionnaire, reviewed the records according to National Diabetes Data Group (NDDG) criteria.<sup>9</sup> The diagnosis of type 2 diabetes was confirmed in 61 (98%) of 62 women. Our primary analyses were based on self-reported diabetes. A secondary set of analyses was conducted that included only women with "definite" type 2 diabetes by the NDDG criteria. We used the NDDG diagnostic criteria because the analytic cohort preceded the American Diabetes Association's diagnostic guidelines published in 1997.<sup>10</sup>

### ASCERTAINMENT OF END POINTS

The primary end points included deaths from all causes and fatal CHD that occurred after the return of the 1976

Women who had both diabetes and CHD were more likely to have hypertension and high cholesterol levels and less likely to use postmenopausal hormone therapy and vitamin E supplements. Women with a history of CHD, regardless of their diabetes status, were older and more likely to have a family history of CHD. On the other hand, women with a history of diabetes, regardless of CHD status, were heavier and drank less alcohol. Women with both diabetes and CHD were more likely to be treated with insulin than those with diabetes alone. Dietary intakes of fiber, fat, and cholesterol did not differ appreciably across the groups.

### ANALYSES ACCORDING TO HISTORY OF DIABETES AND CHD AT BASELINE (1976)

At baseline in 1976, 1437 women reported diagnoses of diabetes (all these women were older than 30 years at diagnosis) and 394 reported diagnoses of MI. **Table 2** shows RRs of death from all causes, all cardiovascular disease, and fatal CHD according to diabetes and CHD status at baseline. The age-adjusted RR of all-cause mortality was approximately 7 times higher for women who had both diabetes and CHD compared with those with neither condition. The age-adjusted RR of death was 3.39

for women with a history of diabetes and no CHD compared with 3.00 for women with a history of CHD and no diabetes. Multivariate adjustment for smoking, body mass index, and other covariates somewhat attenuated these RRs. The multivariate-adjusted RRs of fatal CHD were similar for women with prior CHD (RR, 8.15; 95% confidence interval [CI], 6.25-10.6) and those with diabetes alone (RR, 7.48; 95% CI, 6.30-8.89). Women with both conditions were approximately 18 times more likely to die of CHD than those with neither conditions at baseline (multivariate RR, 17.6; 95% CI, 10.5-29.4).

### ANALYSES ACCORDING TO UPDATED STATUS OF DIABETES AND CHD

During the follow-up periods, an additional 6046 women reported newly diagnosed diabetes (all these women were older than 30 years at diagnosis), and 2473 women reported newly diagnosed CHD. **Table 3** shows RRs of all-cause mortality, fatal CHD, and cardiovascular death according to diabetes and CHD diagnoses at baseline and during follow-up (updated every 2 years). Compared with women with neither diabetes nor CHD, multivariate RRs of all-cause mortality were 2.44 for women with diabe-

questionnaire but before June 1, 1996. Deaths were reported by next of kin and the postal system or ascertained through the National Death Index. We estimate that follow-up for the deaths was more than 98% complete.<sup>11</sup> We obtained copies of death certificates and medical records and determined causes of death (classified according to the categories of the *International Classification of Diseases, Ninth Revision* [ICD-9]).

Fatal CHD was confirmed by hospital records or autopsy or if CHD was listed as the cause of death on the death certificate and evidence of previous CHD was available. Probable fatal CHD cases were designated where CHD was the underlying cause on the death certificate, but no records were available. These cases constituted 14.7% of fatal CHD cases. We also included sudden deaths (12.3% of fatal CHD). Deaths owing to all cardiovascular disease included ICD-9 codes 390 through 459 and 795.

## STATISTICAL ANALYSIS

We conducted 2 sets of analyses, one comparing deaths from all causes and fatal CHD according to reported diabetes and CHD diagnoses at baseline (1976) and the other according to reported diagnoses either at baseline or during follow-up (updated every 2 years). Person-time for each participant was calculated from the date of return of the 1976 questionnaires to the date of confirmed fatal CHD, death from other causes, or June 1, 1996, whichever came first.

We calculated rates of fatal CHD for women with prior diabetes, CHD, or both by dividing the number of incident cases by the number of person-years of follow-up. The relative risk (RR) was computed as the rate among women with prior diabetes, CHD, or both divided by the rate among women with neither condition, with adjustment for 5-year age categories. For the analysis of overall mortality, person-time was calculated from the date of the 1976 questionnaire to the date of death from any cause or June 1, 1996. Duration of clinical diabetes was calculated as years since first diagnosis of

diabetes and the variable was divided into 5 categories ( $\leq 5$ , 6-10, 11-15, 16-25,  $> 25$  years). We collapsed the last 2 categories in the analysis of duration of diabetes stratified by prior CHD. Test for trend was conducted by treating the original duration variable as a continuous variable.

We used pooled logistic regression to adjust estimated incidence rate ratios simultaneously for potential confounding variables. In this approach, independent 2-year blocks of person-time of follow-up are pooled for regression analysis, and the dependence of the incidence rates on time is modeled nonparametrically with indicator variables. D'Agostino et al<sup>12</sup> have showed that the pooled logistic model is asymptotically equivalent to the Cox regression when the time intervals are short and the probability of outcome in the intervals is low (both assumptions are satisfied by our data); examples comparing the 2 methods were given by Cupples et al.<sup>13</sup> Our covariates included age (5-year categories); body mass index, a measure of weight in kilograms divided by the square of height in meters ( $< 21$ , 21-22.9, 23-24.9, 25-28.9, 29-31.9,  $\geq 32$ ); cigarette smoking (never, past, and current smoking of 1 to 14, 15 to 24, and  $\geq 25$  cigarettes per day); menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, postmenopausal with current hormone replacement); and parental history of MI before the age of 60 years. We did not adjust for history of hypertension or hypercholesterolemia because they are considered intermediate variables in the biological pathway. Secondary analysis further adjusting for these variables did not materially change the RRs for total mortality but somewhat attenuated the RRs for fatal CHD. All covariates except parental history of MI were updated every 2 years. Alcohol use and physical activity were first assessed in 1980. Because further analyses adjusting for these 2 variables did not alter the results, we did not include them in the final model. As preplanned, we conducted stratified analyses according to age group, history of hypertension, high cholesterol levels, and parental history of MI.

tes alone, 2.58 for women with CHD alone, and 5.82 for women with both conditions. Compared with women with neither conditions, women with both diabetes and prior CHD were 20 times more likely to die from any cardiovascular disease and 25 times more likely to die from CHD. In contrast to results from Table 2, the RRs of cardiovascular death and fatal CHD were substantially greater for women with CHD alone than those with diabetes alone. The multivariate RRs of fatal CHD were 10.7 (95% CI, 9.03-12.6) for women with CHD alone compared with 5.65 (95% CI, 4.83-6.60) for women with diabetes alone. Restriction of the analyses to only patients with diabetes confirmed by the supplementary questionnaires did not appreciably alter the results. (The age-adjusted RRs of fatal CHD were 12.0 for women with CHD alone and 6.19 for women with diabetes alone.)

In subgroup analyses, the excess risk of fatal CHD associated with diabetes alone, prior CHD alone, or both was significant in all subgroups stratified by age group, history of hypertension, history of high cholesterol levels, or parental history of MI (**Table 4**). Compared with younger women ( $< 55$  years) with neither condition, the RR of fatal CHD for older women ( $\geq 65$  years) with both diabetes and existing CHD was 159.5 (95% CI, 111.1-229.1). As ex-

pected, history of hypertension and parental history of MI augmented the elevated RRs associated with diabetes alone or prior CHD. Interestingly, for women who had diabetes or CHD, high cholesterol levels did not appear to further increase the risk of fatal CHD. One possible explanation is that cholesterol-lowering treatment may have already reduced the risk among those patients.

## THE IMPACT OF DURATION OF CLINICAL DIABETES

The risk of CHD mortality increased monotonically with increased duration of clinical diabetes (**Figure 1**). Compared with nondiabetic women, the RRs of fatal CHD across categories of duration of diabetes ( $\leq 5$ , 6-10, 11-15, 16-25,  $> 25$  years) were 2.75, 3.63, 5.51, 6.38, and 11.9 ( $P < .001$  for trend). In the same multivariate model, the RR of fatal CHD for women with vs without prior CHD was 5.49. The increased risk of fatal CHD with longer duration of diabetes, especially among those with diabetes for 15 years or more, was persistent in women with or without prior CHD (**Figure 2**). Women with prior CHD alone had a RR of 8.61 (95% CI, 7.08-10.5), which was similar to that among women with diabetes for more

**Table 1. Distribution of Potential Coronary Risk Factors According to History of Diabetes and Coronary Heart Disease (CHD) in 1986\***

Risk Factor	No Diabetes and No CHD	Diabetes and No CHD	CHD and No Diabetes	Diabetes and CHD
No. of women	109 231	3705	1302	234
Current smokers, %	23.6	21.0	27.1	19.4
History of hypertension, %	23.1	55.9	47.7	77.4
History of hypercholesterolemia, %	11.2	28.2	32.9	55.0
Parental MI before 60 y, %	20.0	24.1	31.1	29.4
Insulin treatment, %†	...	25.8	...	33.9
Oral hypoglycemic medications, %†	...	32.4	...	27.5
Current postmenopausal hormone use among postmenopausal women, %	19.0	17.1	19.4	14.3
Multivitamin use, %	42.5	41.9	38.4	35.8
Vitamin E supplement use, %	16.2	15.0	12.6	9.2
Age, mean, y	59.9	63.1	65.1	65.8
Alcohol use, mean, g/d	6.3	3.0	6.0	1.5
BMI, mean	25.2	29.8	26.7	30.4
Hours of moderate or vigorous exercise per week, mean	3.1	2.8	2.8	2.7
Dietary fiber intake, mean, g/d	19.1	19.9	20.0	20.1
Saturated fat intake, mean, % energy	11.7	12.0	11.1	11.2
Polyunsaturated fat intake, mean, % energy	6.2	6.2	5.9	5.9
Trans fat intake, mean, % energy	1.7	1.7	1.5	1.6
Dietary cholesterol intake, mean, mg/1000 kcal	150	168	148	164

\*The year 1986 was used in this analysis to represent the overall follow-up of the cohort (1976-1996). Percentages and means for variables other than age are standardized according to the age distribution of the overall study group. MI indicates myocardial infarction; BMI, body mass index (a measure of weight in kilograms divided by the square of height in meters).

†Reported in the supplementary questionnaire or 1998 main questionnaire.

**Table 2. Relative Risks of Death From All Causes, CHD, and All Cardiovascular Disease According to History of Diabetes and Prior CHD at Baseline in 1976: The Nurses' Health Study, 1976-1996\***

Type of Death	No Diabetes and No CHD	Diabetes and No CHD	CHD and No Diabetes	Diabetes and CHD
Deaths from all causes				
No. of cases	7853	458	123	30
Person-years	2 300 753	31 641	7997	948
RR (95% CI)				
Age adjusted	1.0	3.39 (3.08-3.73)	3.00 (2.50-3.60)	6.84 (4.71-9.95)
Multivariate†	1.0	3.12 (2.83-3.44)	2.55 (2.12-3.07)	5.08 (3.47-7.43)
All cardiovascular deaths‡				
No. of cases	1582	216	75	19
RR (95% CI)				
Age adjusted	1.0	7.51 (6.50-8.67)	8.40 (6.63-10.6)	19.9 (12.5-31.8)
Multivariate	1.0	6.59 (5.69-7.63)	6.58 (5.19-8.36)	13.6 (8.45-21.8)
Fatal CHD				
No. of cases	1001	161	61	16
RR (95% CI)				
Age adjusted	1.0	8.70 (7.35-10.3)	10.6 (8.14-13.8)	25.8 (15.6-42.9)
Multivariate	1.0	7.48 (6.30-8.89)	8.15 (6.25-10.6)	17.6 (10.5-29.4)

\*CHD indicates coronary heart disease; RR, relative risk; and CI, confidence interval.

†Models include the following: age (5-year category); time (10 periods); body mass index, a measure of weight in kilograms divided by the square of height in meters ( $<21$ , 21-22.9, 23-24.9, 25-28.9, 29-31.9,  $\geq 32$ ); cigarette smoking (never, past, and current smoking of 1 to 14, 15 to 24, and  $\geq 25$  cigarettes per day); menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, postmenopausal with current hormone replacement); and parental history of myocardial infarction before 60 years of age.

‡Deaths due to all cardiovascular disease included *International Classification of Diseases, Ninth Edition* codes 390 through 459 and 795.

than 15 years (RR, 8.66; 95% CI, 6.87-10.9). A combination of CHD and a long duration of diabetes (ie,  $>15$  years) identifies a particularly high-risk group for fatal CHD (RR, 30.0; 95% CI, 20.7-43.5).

In contrast to the monotonic increased risk of fatal CHD with longer duration of diabetes, the risk of fatal CHD increased dramatically in the first several years after onset of an MI and then remained relatively stable; compared with women without a prior MI, the multi-

variate RRs of fatal CHD across categories of number of years after first MI ( $\leq 5$ , 6-10, 11-20,  $>20$  years) were 4.70, 6.05, 6.12, and 6.74, respectively.

#### COMMENT

In this large prospective cohort of women, type 2 diabetes mellitus was associated with dramatically increased mortality from all causes and fatal CHD among women.



**Table 3. Relative Risks of Death From All Causes, CHD, and All Cardiovascular Disease According to the Status of Diabetes and CHD at Baseline and During Follow-up: The Nurses' Health Study, 1976-1996\***

Type of Death	No Diabetes and No CHD	Diabetes and No CHD	CHD and No Diabetes	Diabetes and CHD
Deaths from all causes				
No. of cases	6939	878	408	239
Person-years	2 231 377	76 356	27 169	6435
RR (95% CI)				
Age adjusted	1.0	2.47 (2.30-2.65)	2.75 (2.48-3.04)	6.12 (5.34-7.00)
Multivariate†	1.0	2.44 (2.27-2.63)	2.58 (2.33-2.87)	5.82 (5.07-6.69)
All cardiovascular deaths				
No. of cases	1188	325	221	158
RR (95% CI)				
Age adjusted	1.0	5.11 (4.51-5.80)	8.23 (7.10-9.54)	22.1 (18.6-26.3)
Multivariate	1.0	4.86 (4.27-5.52)	7.46 (6.43-8.66)	20.1 (16.8-24.1)
Fatal CHD				
No. of cases	697	231	189	122
RR (95% CI)				
Age adjusted	1.0	6.19 (5.32-7.20)	12.0 (10.2-14.2)	29.0 (23.7-35.5)
Multivariate	1.0	5.65 (4.83-6.60)	10.7 (9.03-12.6)	25.3 (20.6-31.1)

\*CHD indicates coronary heart disease; RR, relative risk; and CI, confidence interval. The diagnoses of diabetes and CHD were updated every 2 years.

†Models include the following: age (5-year category); time (10 periods); body mass index (5 categories); cigarette smoking (never, past, and current smoking of 1 to 14, 15 to 24, and  $\geq 25$  cigarettes per day); menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, postmenopausal with current hormone replacement); and parental history of myocardial infarction before 60 years of age.

**Table 4. Multivariate Relative Risks (95% Confidence Intervals) of CHD Death According to the Status of Diabetes and CHD at Baseline and During Follow-up: Subgroup Analysis\***

	No Diabetes and No CHD	Diabetes and No CHD	CHD and No Diabetes	Diabetes and CHD
Age groups, y†				
<55 (n = 250)	1.0 (Referent)	9.19 (6.39-13.2)	29.2 (19.7-43.3)	87.0 (51.3-147.4)
55-64 (n = 591)	3.92 (3.16-4.88)	21.5 (16.4-28.3)	44.4 (33.3-58.9)	105.5 (75.3-148.0)
$\geq 65$ (n = 398)	8.83 (6.81-11.4)	42.7 (31.4-58.1)	66.3 (47.8-92.0)	159.5 (111.1-229.1)
History of hypertension				
No (n = 419)	1.0 (Referent)	5.51 (3.97-7.63)	15.3 (11.6-20.2)	51.5 (32.1-82.6)
Yes (n = 820)	3.45 (2.95-4.03)	13.3 (10.9-16.2)	23.0 (18.5-28.7)	48.8 (38.2-62.2)
History of high cholesterol levels				
No (n = 732)	1.0 (Referent)	5.68 (4.61-6.99)	11.8 (9.30-14.9)	32.0 (22.7-45.3)
Yes (n = 507)	1.42 (1.19-1.69)	7.09 (5.71-8.81)	12.1 (9.65-15.1)	27.3 (21.2-35.1)
Parental history of myocardial infarction				
No (n = 927)	1.0 (Referent)	5.86 (4.92-6.98)	11.1 (9.05-13.5)	26.5 (20.7-33.8)
Yes (n = 312)	1.65 (1.38-1.97)	8.22 (6.14-11.0)	16.1 (12.3-21.0)	37.4 (26.7-52.3)

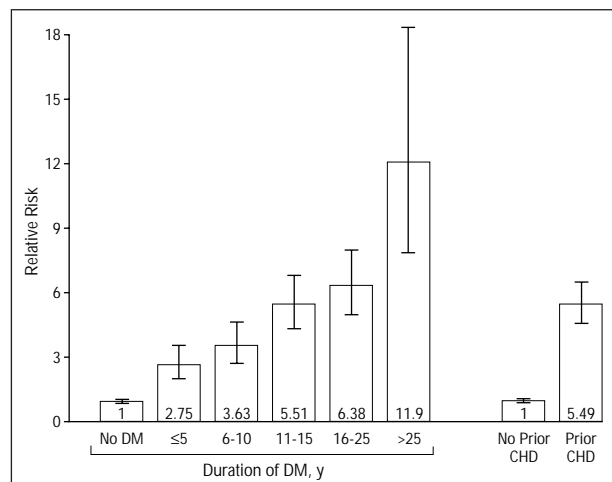
\*Adjusted for the same variables as in Table 3; n indicates the number of coronary heart disease (CHD) deaths. The total number of fatal CHD cases does not add to 1239 because of missing data on menopausal status.

†Age was entered as a continuous variable in the stratified analyses.

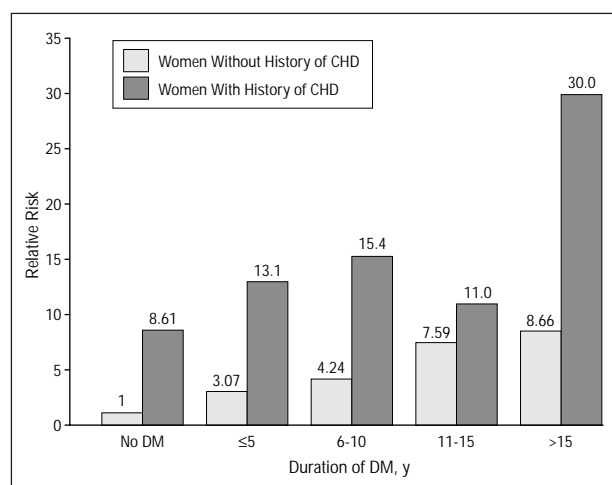
We observed a strong monotonic relationship between duration of clinical diabetes and CHD mortality, independent of history of CHD. The combination of a long duration of diabetes and preexisting CHD identifies a particularly high-risk group.

Several previous studies have compared the magnitude of CHD risk associated with history of diabetes or prior CHD. Haffner et al<sup>4</sup> followed up 2432 Finnish men and women aged 45 to 64 years for 7 years and found that the risk of fatal CHD was as high among diabetic patients without prior CHD as it was among nondiabetic patients who had experienced prior CHD. Because the study involved only 69 nondiabetic patients with prior CHD, the power of the study to detect differences between the 2 groups was limited. Also, the small sample

size did not allow separate analyses by sex or stratification by duration of diabetes. In a 5-year follow-up of 91 285 US male physicians aged 40 to 84 years, Lotufo et al<sup>14</sup> found that for all-cause mortality, the magnitude of excess risk conferred by diabetes was similar to that conferred by prior CHD. For fatal CHD, however, prior CHD was a more powerful predictor (age-adjusted RR was 3.3 for diabetic men without prior CHD vs 5.6 for nondiabetic men with prior CHD). The discrepancy of the results between the 2 studies may be due to different age distribution and sex composition of the 2 populations. The duration of diabetes may also be different in the 2 studies; the average duration of diabetes was 8 years in the Finnish study, whereas the duration of diabetes was not ascertained in the Physicians' Health Study. Re-



**Figure 1.** Multivariate relative risks and 95% confidence intervals of fatal coronary heart disease (CHD) associated with duration of diabetes mellitus (DM) and a prior history of CHD. Adjusted for the same covariates as in Table 2.



**Figure 2.** Multivariate relative risks of fatal coronary heart disease (CHD) according to duration of diabetes mellitus (DM) stratified by a prior history of CHD. Adjusted for the same covariates as in Table 2.

cently, Malmberg and colleagues<sup>5</sup> reported that in a 2-year study diabetic patients (duration of diabetes was not specified) without prior cardiovascular disease had rates of coronary morbidity and mortality similar to those for nondiabetic patients with previous vascular disease.

In our baseline analyses (Table 2), the excess risk of cardiovascular death and fatal CHD conferred by diabetes alone was similar to that conferred by prior CHD. However, in the updated analyses (Table 3), the excess risk of fatal CHD associated with preexisting CHD was substantially greater than that conferred by diabetes without clinical CHD. Obviously, in the baseline analyses, only women who had a long duration of diabetes ( $\geq 20$  years) were included in the diabetic group, whereas in the updated analyses, both new and long-standing cases of diabetes were included. Our findings highlight the importance of considering duration of diabetes when comparing the magnitude of excess risk of fatal CHD conferred by diabetes alone and prior CHD.

Diabetes has more deleterious effects on women than on men; it eliminates the usual female advantage for coro-

nary disease mortality. In the Rancho Bernardo Study,<sup>15</sup> diabetic women had CHD mortality rates similar to both nondiabetic and diabetic men, whereas nondiabetic women had substantially lower risk. The reason for the accelerated atherogenesis among diabetic women is not completely understood, but it is at least in part related to more severe lipid and lipoprotein abnormalities, particularly elevated levels of triglycerides and reduced levels of high-density lipoprotein, among diabetic women.<sup>16,17</sup> A recent study<sup>3</sup> suggests greater impairment of endothelial function associated with type 2 diabetes in women than in men. In addition, the magnitude of increased risk of reinfarction and fatality rate following an acute MI among diabetic patients compared with nondiabetic patients was greater in women than in men.<sup>18</sup>

Our data support current guidelines that recommend aggressive management of cardiovascular risk factors in diabetic patients, including hypertension, dyslipidemia, and lifestyle factors (smoking, obesity, and diet).<sup>19</sup> The United Kingdom Prospective Diabetes Study showed that tight control of blood pressure substantially decreased the risk of diabetes-related deaths and the progression of microvascular complications,<sup>20</sup> providing support for tighter control of blood pressure for diabetic individuals than usually is recommended for nondiabetic individuals with hypertension.

A recent American Diabetes Association guideline<sup>21</sup> recommends the same cholesterol-lowering goal for people with diabetes and no clinical CHD as for patients with preexisting CHD (ie, a low-density lipoprotein cholesterol level  $< 100$  mg/dL [ $< 2.59$  mmol/L]). Two statin trials<sup>22,23</sup> among patients with existing CHD showed similar significant reductions in CHD death in both patients with and without diabetes. A secondary analysis of the Scandinavian Simvastatin Survival Study showed that simvastatin therapy was associated with even greater reductions in risk of major CHD events and total mortality among diabetic patients than among nondiabetic patients.<sup>24</sup> The effects of tight glycemic control on cardiovascular complications are not yet settled, although intensive therapy that lowers blood glucose levels has been proved to reduce risk of microvascular complications in both patients with type 1<sup>25</sup> and type 2<sup>26</sup> diabetes.

Our study is one of few epidemiologic studies on diabetes-related cardiovascular risk among women. The large sample size and long duration of follow-up provide the opportunity to examine the impact of duration of clinical diabetes on risk of cardiovascular disease. The follow-up rate of this cohort was high during 20 years of follow-up (98% for death ascertainment). Thus, our study results are unlikely to be biased by losses to follow-up. In addition, we have collected detailed information on cardiovascular risk factors such as smoking, body mass index, menopausal status, and postmenopausal hormone use through repeated assessments.

Several limitations of the study should be considered. The data on diagnosed diabetes and CHD were based on self-reports by the nurses. This may have led to some misclassification. However, our previous studies<sup>7,8</sup> have found self-reporting of these medical conditions to be reliable. To avoid potential confounding by type 1 diabetes, we included only women reporting a diagnosis of dia-

betes at 30 years or older. Moreover, the analysis restricted to confirmed cases of type 2 diabetes by the supplementary questionnaire yielded similar results.

Because our "nondiabetic" cohort was not uniformly screened for glucose intolerance and the onset of diabetes can occur several years before clinical diagnosis,<sup>27</sup> the reported duration of diabetes in our study may have been underestimated. Also, some cases of diabetes may have been undiagnosed. This misclassification, however, would have inflated the cardiovascular risk in the nondiabetic population and led to underestimation of the RRs among our diabetic population. We believe that the proportion of undiagnosed diabetes is relatively small in our cohort compared with the general population because virtually all participants in our study have ready access to health care. For example, more than 98% of the women in our study visited a physician for a physical examination, breast examination, mammogram, or sigmoidoscopy or colonoscopy at least once between 1988 and 1990. Finally, the diagnostic criteria for type 2 diabetes were changed in 1997<sup>10</sup> such that lower fasting glucose levels ( $\geq 126$  mg/dL [ $\geq 6.99$  mmol/L]) would now be considered diagnostic. We used the criteria proposed by the National Diabetes Data Group<sup>9</sup> because all our cases were diagnosed before June 1996. If the new criteria were used, some women in this study classified as nondiabetic would have been reclassified as having diabetes, and the cardiovascular risk in the reference (nondiabetic) population would have been even lower.

In conclusion, our data indicate that diabetes is associated with dramatically increased risk of total mortality and CHD death among women. The excess risk of fatal CHD for women who had clinical diabetes for more than 15 years was similar to that conferred by prior CHD. The combination of a long duration of diabetes and pre-existing CHD identifies a particularly high-risk group.

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