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

20 Years of Follow-up

Frank B. Hu, MD; Meir J. Stampfer, MD; Caren G. Solomon, MD; Simin Liu, MD; Walter C. Willett, MD; Frank E. Speizer, MD; David M. Nathan, MD; JoAnn E. Manson, MD

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 8,464 deaths from all causes, including 1,239 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 baseline. 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 (<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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Type 2 diabetes mellitus is a well-established risk factor for coronary heart disease (CHD). Diabetic women are at particularly high risk of CHD; 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. Two recent analyses 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. 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.

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 (2,341,338 person-years), we documented 8,464 deaths from all causes, including 1,239 cases of fatal CHD. A total of 1,892 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.
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 type 2 diabetes mellitus. Women with diabetes alone during follow-up (updated every 2 years) were 3.00 for women with both diabetes and CHD compared with 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 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. 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. 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.

ASCERTAINMENT OF END POINTS

The primary end points included deaths from all causes and fatal CHD that occurred after the return of the 1976
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.11 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 793.

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 (≤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 al12 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.13 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, 21.2-22.9, 23.2-24.9, 25-28.9, 29-31.9, ≥32); cigarette smoking (never, past, and current smoking of 1 to 14, 15 to 24, and ≥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.

The risk of CHD mortality increased monotonically with increased duration of clinical diabetes (Figure I). Compared with nondiabetic women, the RRs of fatal CHD across categories of duration of diabetes (≤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 an RR of 8.61 (95% CI, 7.08-10.5), which was similar to that among women with diabetes for more
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 multivariate RRs of fatal CHD across categories of number of years after first MI (<5, 5-10, 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.
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 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-
Diabetes has more deleterious effects on women than on men; it eliminates the usual female advantage for coronary morbidity and mortality. In the Rancho Bernardo Study, 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. A recent study 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.

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). 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, 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 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 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. 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 and type 2 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 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 diabetes.
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, 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 such that lower fasting glucose levels (≥126 mg/dL [≥7.99 mmol/L]) would now be considered diagnostic. We used the criteria proposed by the National Diabetes Data Group 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 preexisting CHD identifies a particularly high-risk group.

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Corresponding author: Frank B. Hu, MD, Department of Nutrition, Harvard School of Public Health, 66 Huntington Ave, Boston, MA 02115 (e-mail: Frank.hu@channing.harvard.edu).

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