

# Elevated Risk of Cardiovascular Disease Prior to Clinical Diagnosis of Type 2 Diabetes

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**OBJECTIVE**— To examine whether the risk of cardiovascular disease (CVD) is elevated before clinical diagnosis of type 2 diabetes in women.

**RESEARCH DESIGN AND METHODS**— A total of 117,629 female nurses aged 30–55 years who were free of diagnosed CVD at baseline were recruited in 1976 and followed for 20 years.

**RESULTS**— A total of 1,508 women had diagnosed type 2 diabetes at baseline in 1976. During 20 years of follow-up, 110,227 women remained free of diabetes diagnosis and 5,894 women developed type 2 diabetes. During 2.2 million person-years of follow-up, we documented 1,556 new cases of myocardial infarction (MI), 1,405 strokes, 815 fatal coronary heart disease (CHD), and 300 fatal strokes. Among women who developed type 2 diabetes during follow-up, the age-adjusted RRs of MI were 3.75 (95% CI 3.10–4.53) for the period before the diagnosis and 4.57 (3.87–5.39) for the period after the diagnosis, compared with women who remained free of diabetes diagnosis. The multivariate RRs further adjusting for BMI, smoking, and other cardiovascular risk factors were 3.17 (2.61–3.85) and 3.97 (3.35–4.71). The risk of stroke was also significantly elevated before diagnosis of diabetes (multivariate RR = 2.30 [1.76–2.99]). Further adjustment for history of hypertension or hypercholesterolemia did not appreciably alter the results.

**CONCLUSIONS**— Our data indicate a substantially elevated risk of CVD before clinical diagnosis of type 2 diabetes in women. These findings suggest that aggressive management of cardiovascular risk factors is warranted in individuals at increased risk for diabetes.

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**C**ardiovascular disease (CVD) is the leading cause of death in individuals with type 2 diabetes, which affects some 15 million Americans (1). Among diabetic individuals, CHD accounts for >50% of all deaths, and stroke accounts for an additional 15% (2). Diabetic women are

at particularly high risk of CVD; diabetes eliminates the usual female advantage for coronary disease mortality (3).

There is some evidence that the risk for CVD starts to increase long before the onset of clinical diabetes, which has led to the “ticking clock” hypothesis (4). In an

8-year follow-up of the San Antonio Heart Study (4), subjects who converted to diabetes during the follow-up had higher baseline levels of total and LDL cholesterol, triglycerides, and blood pressure and lower levels of HDL than those who remained nondiabetic, even after adjustment for obesity. The enhanced atherogenic risk profile in the prediabetic state may contribute to the subsequent increased risk of CVD. To our knowledge, no long-term prospective data exist on incidence of cardiovascular end points in prediabetic subjects. The Nurses’ Health Study (NHS) cohort afforded a unique opportunity to address this issue because of its large size and 20-year follow-up period. Therefore, we examined prospectively the risk of myocardial infarction (MI) or stroke among women who developed type 2 diabetes during follow-up as compared with those in the NHS cohort who remained nondiabetic. In particular, we estimated the risk of developing CVD according to the time from baseline to clinical diagnosis of diabetes (period before diagnosis).

## RESEARCH DESIGN AND METHODS

### Study population

The NHS cohort was established in 1976, when 121,700 female registered nurses aged 30–55 years and residing in 11 large U.S. 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, diabetes, and other illnesses. Women with a history of CHD (including MI, angina, and/or coronary revascularization) or stroke at baseline were excluded. We also excluded the relatively few women with confirmed type 1 diabetes or those whose diabetes was diagnosed at age 30 or younger ( $n = 470$ ); the final population for analyses included 117,629 women.

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**Abbreviations:** CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; NHS, Nurses’ Health Study; NDDG, National Diabetes Data Group.

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

### Confirmation of diabetes

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 with diabetes. A case of diabetes was considered confirmed if at least one of the following was reported on the supplementary questionnaire: 1) one or more classic symptoms (excessive thirst, polyuria, weight loss, hunger, or pruritis) plus fasting plasma glucose  $\geq 140$  mg/dl (7.8 mmol/l) or random plasma glucose  $\geq 200$  mg/dl (11.1 mmol/l); 2) at least two elevated plasma glucose concentrations on different occasions (fasting glucose  $\geq 140$  mg/dl [ $\geq 7.8$  mmol/l] or random plasma glucose  $\geq 200$  mg/dl [ $\geq 11.1$  mmol/l] and/or a concentration  $\geq 200$  mg/dl after  $\geq 2$  h of 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 (5). 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, blinded to the information reported on the supplementary questionnaire, reviewed the records according to National Diabetes Data Group (NDDG) criteria (6). The diagnosis of type 2 diabetes was confirmed in 61 of 62 (98%) of the women. We used the NDDG diagnostic criteria because the analytic cohort preceded the American Diabetes Association's diagnostic guidelines published in 1997 (7). In our primary analyses, we used reported diagnoses of diabetes to define diabetes status. A secondary set of analyses using "definite" type 2 diabetic cases according to the NDDG criteria yielded similar results.

### Ascertainment of end points

The primary end points for this study were incident CHD (defined as nonfatal MI or fatal CHD) and stroke that occurred after the return of the 1976 questionnaire but before 1 June 1996. We requested permission to review medical records from women who reported having a nonfatal MI or stroke on a follow-up questionnaire. Study physicians with no knowledge of the self-reported risk factor status reviewed the records. Nonfatal MI

was confirmed if it met the criteria of the World Health Organization of symptoms plus either diagnostic electrocardiographic changes or elevated cardiac enzyme levels (8). Infarctions that required hospital admission and for which confirmatory information was obtained by interview or letter, but for which no medical records were available, were designated as probable (19%). We included all confirmed and probable cases in the analyses because results were the same after excluding probable cases. Stroke was confirmed by medical records according to the criteria of the National Survey of Stroke (9), requiring a constellation of neurological deficits, sudden or rapid in onset, lasting 24 h or more; events were further subclassified as hemorrhagic stroke (subarachnoid or intraparenchymal), ischemic stroke (thrombotic or embolic), or stroke of unknown cause. The follow-up rate for nonfatal events was 97% of the total potential person-years of follow-up.

Deaths were reported by next of kin and the postal system or ascertained through the National Death Index. Using all sources combined, we estimate that follow-up for the deaths was  $>98\%$  complete (10). Fatal CHD was defined as fatal MI if this was confirmed by hospital records or autopsy, or if CHD was listed as the cause of death on the certificate and this was the underlying and most plausible cause, and evidence of previous CHD was available. The statement of the cause of death on the death certificate was never relied on by itself as providing sufficient confirmation of death due to CHD. We also included sudden death within 1 h of onset of symptoms in women with no other plausible cause other than coronary disease (8% of fatal CHD). Fatal strokes were coded using the same criteria as nonfatal cases, but we accepted autopsy evidence as well as the death certificate listing of cause.

### Statistical analysis

Subjects were categorized into three groups according to clinical diabetes status: nondiabetic throughout the study, diabetic at baseline, and diabetic diagnosed during follow-up. 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 1 June 1996, whichever came first. For women who developed di-

abetes during follow-up, we further divided the follow-up experience into person-years before diagnosis of clinical diabetes and those after the diagnosis. We calculated time from baseline (time) to clinical diagnosis of diabetes (time before diagnosis). Duration of clinical diabetes was calculated as years since first diagnosis of diabetes.

We calculated rates of CHD or stroke for each group of women by dividing the number of incident cases by the number of person-years of follow-up. The relative risks were computed as the rates in baseline or new diabetic subjects divided by the rate among women who remained nondiabetic throughout the study, with adjustment for 5-year age categories. We used pooled logistic regression across the 10 2-year intervals (11), which is asymptotically equivalent to Cox regression with time-varying covariates, to adjust simultaneously for potential confounding variables, including age (5-year categories); BMI ( $<21$ , 21–22.9, 23–24.9, 25–28.9, 29–31.9, and  $\geq 32$  kg/m<sup>2</sup>); cigarette smoking (never, past, and current smoking of 1–14, 15–24, and  $\geq 25$  cigarettes per day); menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement); and parental history of MI before age 60 years. 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 two variables did not change the results, we did not include them in the final model.

**RESULTS**— A total of 1,508 women had diagnosed type 2 diabetes at baseline in 1976. During 20 years of follow-up, 110,227 women remained free of diagnosed diabetes and 5,894 women reported a new diagnosis of type 2 diabetes. For newly diabetic subjects, the average time between baseline and diagnosis was 12 years. Compared with nondiabetic subjects, those with type 2 diabetes at baseline or during follow-up had higher BMI, were more likely to have a parental history of MI, and were less likely to drink alcohol, engage in vigorous exercise, or use postmenopausal hormones (Table 1). Compared with nondiabetic subjects, women with diabetes at baseline were more likely to have hypertension, high

Table 1—Baseline characteristics according to clinical diabetes status

	Nondiabetic throughout the study	Type 2 diabetic at baseline (1976)	New diabetes diagnosed during follow-up (1976–1996)
<i>n</i>	110,227	1,508	5,894
Mean age (years)	42	46	45
Mean BMI (kg/m <sup>2</sup> )	23	28	28
Mean alcohol intake (g/day)*	7	4	4
Hypertension (%)	10	42	27
High cholesterol (%)	3	13	6
Current smoking (%)	33	31	32
Vigorous exercise $\geq 1$ /week (%)*	37	30	30
Family history of diabetes (%)†	15	37	32
Parental history of MI (%)	15	19	18
Current menopausal hormone use among postmenopausal women (%)	25	20	21

\*First assessed in 1980; †assessed in 1982.

cholesterol, and family history of diabetes. The risk profile was intermediate for women who developed diabetes during follow-up.

During 2,238,288 person-years of follow-up, we documented 1,556 new cases of MI, 1,405 new cases of stroke, 815 cases of fatal CHD, and 300 cases of fatal stroke. Compared with nondiabetic subjects, women with diabetes at baseline had dramatically increased risk of CHD (Table 2). The age-adjusted RRs were 5.65 (95% CI 4.60–6.96) for nonfatal MI, 9.01 (7.20–11.3) for fatal CHD, and

6.92 (5.94–8.05) for total CHD. These associations remained strong and significant even after adjustment for cardiovascular risk factors.

Among women who developed type 2 diabetes during follow-up, the age-adjusted RRs of MI were 3.75 (95% CI 3.10–4.53) for the period before the diagnosis and 4.57 (3.87–5.39) for the period after the diagnosis. The multivariate RRs were 3.17 (2.61–3.85) and 3.97 (3.35–4.71), respectively. The multivariate RR of fatal CHD after diagnosis of diabetes was 2.14 (1.72–2.66). By defini-

tion, fatal events could not occur before diagnosis of diabetes.

Compared with nondiabetic subjects, the prediabetic stage was also associated with elevated risk of stroke, although women with diabetes at baseline had the highest risk of stroke. The multivariate adjusted RRs of stroke were 4.56 (95% CI 3.63–5.73) for women with diabetes at baseline and 3.07 (2.53–3.73) for the period after the diagnosis (Table 3). Similar patterns of results were obtained when we analyzed MI and stroke as a combined end point (Fig. 1).

We did not adjust for history of hypertension or hypercholesterolemia because we considered these to be intermediate variables in the biological pathway to CVD. As expected, secondary analysis further adjusting for these variables somewhat attenuated the associations. Compared with nondiabetic subjects, the multivariate RRs of MI or stroke were 2.59 (95% CI 2.23–3.01) before diagnosis of diabetes, 3.24 (2.85–3.68) after the diagnosis, and 3.91 (3.34–4.57) for diabetes present at baseline.

We conducted stratified analyses according to family history of diabetes and BMI. Among women without a family history of diabetes, the multivariate RRs of MI or stroke were 3.07 (95% CI 2.55–3.68) for prediabetic phase, 3.55 (3.01–4.19) after diagnosis of diabetes, 4.77 (3.85–5.92) for diabetes present at base-

Table 2—RRs of CHD according to clinical diabetes status: the NHS 1976–1996

	Nondiabetic throughout the study	Diabetic at baseline (1976)	New diabetes diagnosed at follow-up	
			RRs prior to diagnosis	RRs after the diagnosis
<b>Nonfatal MI</b>				
<i>n</i>	1,164	99	124	169
Person-years	2,103,936	25,352	66,939	42,061
Age-adjusted	1.0	5.65 (4.60–6.96)	3.75 (3.10–4.53)	4.57 (3.87–5.39)
Multivariate*	1.0	5.28 (4.28–6.52)	3.17 (2.61–3.85)	3.97 (3.35–4.71)
<b>Fatal CHD</b>				
<i>n</i>	626	89	—	100
Age-adjusted	1.0	9.01 (7.20–11.3)	—	2.56 (2.07–3.16)
Multivariate	1.0	7.42 (5.91–9.32)	—	2.14 (1.72–2.66)
<b>Total CHD</b>				
<i>n</i>	1,790	188	—	269
Age-adjusted	1.0	6.92 (5.94–8.05)	—	4.56 (4.00–5.20)
Multivariate	1.0	6.21 (5.32–7.25)	—	3.93 (3.43–4.51)

Data are *n*, RR, and RR (95% CI). \*Models include the following: age (5-year category); time period (10 periods); BMI (<21, 21–22.9, 23–24.9, 25–28.9, 29–31.9, and  $\geq 32$  kg/m<sup>2</sup>); cigarette smoking (never, past, and current smoking of 1–14, 15–24, and  $\geq 25$  cigarettes/day); menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement); and parental history of MI before 60 years of age.

Table 3—RRs of stroke according to clinical diabetes status: the NHS 1976–1996

	Nondiabetic throughout the study	Diabetic at baseline (1976)	New diabetes diagnosed at follow-up	
			RRs prior to diagnosis	RRs after the diagnosis
Nonfatal stroke				
<i>n</i>	882	61	59	103
Person-years	2,103,936	25,352	66,939	42,061
Age-adjusted	1.0	4.53 (3.49–5.88)	2.53 (1.94–3.31)	3.34 (2.72–4.11)
Multivariate*	1.0	4.41 (3.43–5.67)	2.30 (1.76–2.99)	3.15 (2.56–3.88)
Fatal stroke				
<i>n</i>	259	21	—	20
Age-adjusted	1.0	5.43 (3.48–8.51)	—	1.29 (0.85–2.03)
Multivariate	1.0	5.25 (3.34–8.24)	—	1.38 (0.87–2.20)
Total Stroke				
<i>n</i>	1,141	82	—	123
Age-adjusted	1.0	4.74 (3.78–5.94)	—	3.17 (2.62–3.83)
Multivariate	1.0	4.56 (3.63–5.73)	—	3.07 (2.53–3.73)

Data are *n*, RR, and RR (95% CI). \*Models include the following: age (5-year category); time period (10 periods); BMI (<21, 21–22.9, 23–24.9, 25–28.9, 29–31.9, and ≥32 kg/m<sup>2</sup>); cigarette smoking (never, past, and current smoking of 1–14, 15–24, and ≥25 cigarettes/day); menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement); and parental history of MI before 60 years of age.

line. Among women with a family history of diabetes, the corresponding RRs were 2.25 (4.63–3.10), 3.63 (2.87–4.59), and 4.90 (3.75–6.40), respectively. In addition, the significantly elevated risk of MI or stroke associated with the prediabetic phase appeared to be stronger for non-obese (BMI <30) women (RR = 3.84 [3.18–4.62]) than for obese women (RR = 1.79 [1.34–2.39]).

For the prediabetic stage, we divided women into three groups according to time before clinical diagnosis of diabetes. Compared with nondiabetic women, the RRs of MI or stroke according to time before clinical diagnosis of diabetes (≥15, 10–14.9, and <10 years) were 2.40 (95% CI 1.91–3.01), 3.19 (2.44–4.16), and 3.64 (3.19–4.16), respectively (Fig. 2).

**CONCLUSIONS**— In this large prospective cohort study of women, we found a significantly elevated risk of MI and stroke before clinical diagnosis of type 2 diabetes, as compared with women who remained nondiabetic throughout the study. The increased risk was persistent among both obese and nonobese women and those with or without a family history of diabetes. The risk for CVD began to increase at least 15 years before diabetes diagnosis. The risk for CVD increased further after clinical diagnosis of diabetes, and the highest incidence was

found among women whose diabetes was diagnosed at baseline in 1976 and who thus had longer duration of diabetes.

Our findings provide support for the “ticking clock” hypothesis, which postulates that “the clock for coronary heart disease starts ticking before the onset of clinical diabetes” (4). They are also compatible with the “common soil” hypothesis (12), which postulates that both diabetes and CVD have common genetic and environmental antecedents, i.e., “they spring from a ‘common soil.’” Con-

sistent with several previous studies (4,13,14), subjects in our study who converted to type 2 diabetes during follow-up had a more atherogenic risk profile (e.g., higher BMI values and greater prevalence of hypertension and hypercholesterolemia) than nondiabetic women throughout the study, although women with diabetes at baseline (and thus the longest duration of diabetes) had the most adverse cardiovascular risk profile. The elevated cardiovascular risk before diagnosis of diabetes, however, was not fully ex-

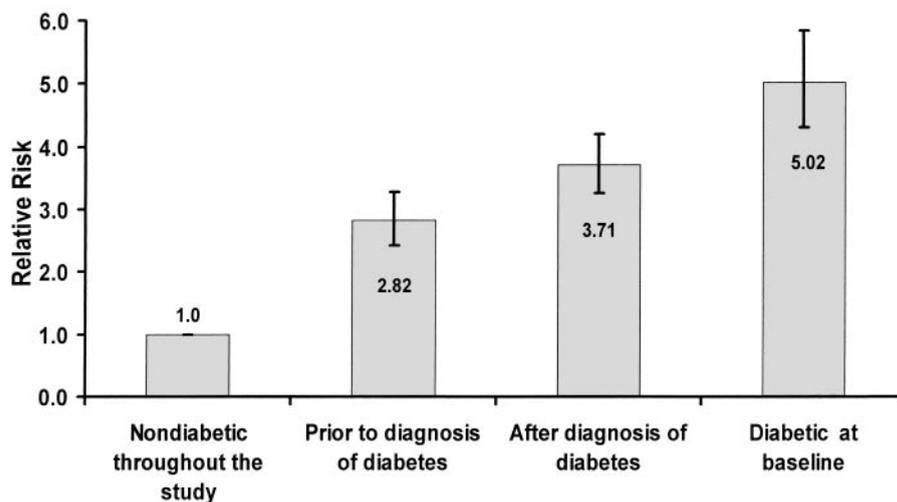
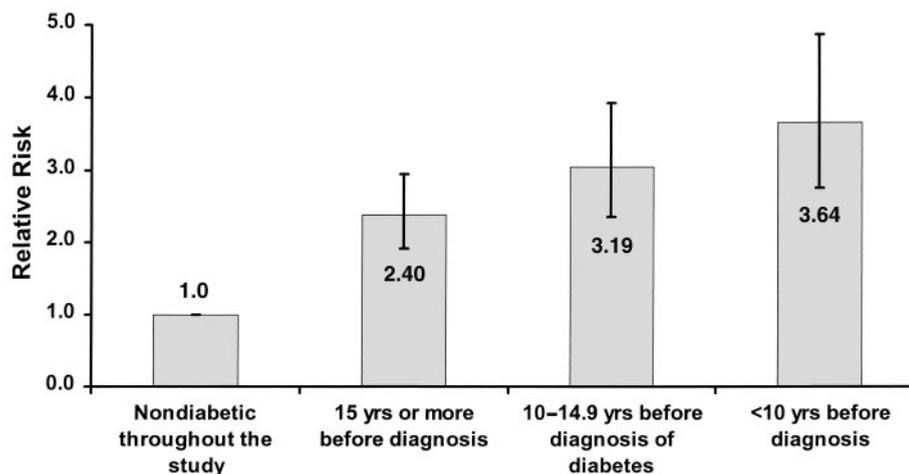


Figure 1—Multivariate RRs and 95% CIs of MI or stroke according diabetes status: the NHS 1976–1996. Adjusted for the same variables in Table 2.



**Figure 2**—Multivariate RRs and 95% CIs of MI or stroke according to time before clinical diagnosis of diabetes. Adjusted for the same variables in Table 2.

plained by the differences in conventional cardiovascular risk factors between nondiabetic and newly diabetic subjects. A caveat of our study is that we did not measure lipoprotein composition and particle size. Also, we did not have measures of other cardiovascular risk factors, such as homeostatic factors, markers of inflammation, and insulin levels, which may also be elevated in the prediabetic state.

An alternative explanation for the increased risk before clinical diagnosis of diabetes is the delayed diagnoses of type 2 diabetes in the “prediabetic” group. In the general population, up to 50% of type 2 diabetic cases are inadequately diagnosed (1,15). It has been estimated that onset of type 2 diabetes occurs at least 4–7 years before clinical diagnosis (15), although the lowering of the threshold for diagnosis of type 2 diabetes by the recent American Diabetes Association criteria may have reduced the rate of undiagnosed diabetes (7). In our study, however, the risk for CVD was significantly elevated even 15 years before the diagnosis, suggesting that undiagnosed diabetes is unlikely to explain our results. In addition, because our participants were all health professionals, we believe that undiagnosed diabetes is relatively rare in our cohort compared with the general population. Unlike many Americans, virtually all participants in our study have ready access to health care. Of the women in our cohort, >98% visited a physician at least once between 1988 and 1990.

The increased CVD risk in the prediabetic state may be due, in part, to a

greater proportion of subjects with impaired glucose tolerance in the prediabetic group than in the persistent nondiabetic group. However, the positive association was persistent even among women who were less likely to have impaired glucose tolerance (e.g., women without a family history of diabetes or nonobese women). Also, in the San Antonio Heart Study (4), the increased cardiovascular risk factors did not diminish after eliminating subjects with impaired glucose tolerance.

To our knowledge, our study is the first to document increased risk of cardiovascular end points before clinical diagnosis of type 2 diabetes. The large sample size and long duration of follow-up provide adequate power to both compare CVD risk according to diabetes status and conduct subgroup analyses. The follow-up rate of this cohort was high over 20 years of follow-up (98% for death ascertainment). Thus, study results are unlikely to be biased by losses to follow-up. Covariate information, including smoking, BMI, and postmenopausal hormone use, was updated biennially.

In conclusion, we found a substantially elevated risk of MI or stroke before clinical diagnosis of type 2 diabetes in women. The risk for CVD increased further after clinical diagnosis of diabetes. Our data provide support for the hypothesis that cardiovascular risk begins to increase long before overt diabetes develops. These findings suggest that aggressive management of cardiovascular

risk factors is warranted in individuals at increased risk for diabetes.

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