Prospective Study of Type 1 and Type 2 Diabetes and Risk of Stroke Subtypes

The Nurses' Health Study

Mohsen Janghorbani, phd[1,2]
Frank B. Hu, md[2,3]
Walter C. Willett, md[2,3,4]
Tricia Y. Li, md[2]
Joann E. Manson, md[3,4,5]
Giancarlo Logroscino, md[3]
Kathryn M. Rexrode, md[4,5]

OBJECTIVE — The aim of this study was to examine the relationship between type 1 and type 2 diabetes and risk of stroke subtypes in women.

RESEARCH DESIGN AND METHODS — We followed 116,316 women aged 30–55 years in 1976 through 2002 for incidence of stroke. At baseline and through biennial follow-up, women were asked about their history and treatment of diabetes and other potential risk factors for stroke.

RESULTS — During 2.87 million person-years of follow-up, 3,463 incident strokes occurred. In multivariate analyses, the incidence of total stroke was fourfold higher in women with type 1 diabetes (relative risk [RR] 4.7 [95% CI 3.3–6.6]) and twofold higher among women with type 2 diabetes (1.8 [1.7–2.0]) than for nondiabetic women. The multivariate RR of ischemic stroke was increased sixfold (6.3 [4.0–9.8]) in type 1 diabetes and twofold (2.3 [2.0–2.6]) in type 2 diabetes. Risks for large-artery infarction and lacunar stroke were similar. Type 1 diabetes was also significantly associated with the risk of hemorrhagic stroke (3.8 [1.2–11.8]), but type 2 diabetes was not (1.0 [0.7–1.4]).

CONCLUSIONS — Both type 1 and type 2 diabetes are associated with substantially increased risks of total and most subtypes of stroke.

Diabetes Care 30:1730–1735, 2007

In many (1–11) but not all (12–15) epidemiological studies, type 2 diabetes has been an important risk factor for ischemic stroke; however, relative risks (RRs) have varied widely, from 1.3 to 4.9 (1–11). The disparate RRs may be explained in part by differences in populations, definitions of diabetes, types of stroke studied, and analytical methods. The increased risk of stroke has been linked to the pathophysiological changes seen in the cerebral vessels of individuals with diabetes (1). In contrast, the association with hemorrhagic stroke remains controversial; reported associations have been positive (3,5), null (16,17), or even inverse (1,18–20). Further, only a few small studies have examined the risk of stroke in patients with type 1 diabetes (18–21), and this relationship remains unsettled. We used the large ongoing Nurses' Health Study to examine the risk of total stroke and its subtypes in women with type 1 or type 2 diabetes.

From the [1]Department of Epidemiology and Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran; the [2]Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts; the [3]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; the [4]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; and the [5]Division of Preventive Medicine, Brigham and Women's Hospital, Boston, Massachusetts.

Address correspondence and reprint requests to Mohsen Janghorbani, Department of Epidemiology and Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: janghorbani@yahoo.com.

Received for publication 18 November 2006 and accepted in revised form 20 March 2007.

Published ahead of print at http://care.diabetesjournals.org on 27 March 2007. DOI: 10.2337/dc06-2363.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

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

RESEARCH DESIGN AND METHODS

Data collection

The Nurses' Health Study is an ongoing cohort established in 1976 when 121,701 female registered nurses aged 30–55 years completed a mailed questionnaire on their health status and various lifestyle and behavioral risk factors. Participants complete biennial follow-up questionnaires to update risk factors and report newly diagnosed diseases including stroke. The biennial follow-up rate exceeds 90%, and mortality follow-up is estimated as >98% complete (22). The human research committees at the Harvard School of Public Health and Brigham and Women's Hospital approved the study.

Ascertainment of stroke

Incident strokes were defined as the first nonfatal stroke or stroke death occurring after the baseline questionnaire in 1976 but before 1 June 2002. Women who reported a stroke were asked for permission to access their medical records, which were reviewed by a physician without knowledge of the participant's exposure status. Women for whom medical record release was refused or for whom medical records were unavailable were classified as probable if supporting information was provided. Cerebrovascular pathology due to infection, trauma, or malignancy was excluded, as were "silent" strokes discovered only by radiological imaging. Stroke was classified according to criteria established by the National Survey of Stroke (23), which required evidence of a neurological deficit with sudden or rapid onset that persisted for >24 h or until death. Strokes were classified as follows: ischemic stroke (thrombotic or embolic strokes), hemorrhagic stroke (subarachnoid or intraparenchymal hemorrhage), or stroke of unknown subtype. For each type of stroke, a definite diagnosis was made when a CT scan, MRI, angiography, surgery, or autopsy confirmed the lesion; otherwise a probable diagnosis was made. CT or MRI reports were available for 89% of those with medical records.

Table 1—*Age-adjusted characteristics* of women (116,316) by diabetes status, the Nurses' Health Study, 1976–2002*

Characteristic	Without diabetes	Type 1 diabetes	Type 2 diabetes
n	105,247	303	10,766
Age (years)	53.8 ± 10.3	52.4 ± 10.3	55.3 ± 10.0
Age at stroke (years)	67.8 ± 8.3	63.4 ± 8.0	67.6 ± 7.3
Height (cm)	163.6 ± 8.4	163.3 ± 12.1	163.3 ± 9.0
BMI at age 18 (kg/m^2)	21.2 ± 2.9	21.4 ± 3.2	22.4 ± 3.8
BMI (kg/m^2)	25.0 ± 4.6	24.3 ± 4.8	29.8 ± 6.0
Weight change since age 18 (kg)	2.0 ± 11.1	0.68 ± 11.3	5.9 ± 13.2
Duration of diabetes (years)	—	31.4 ± 14.3	11.4 ± 9.5
Daily alcohol intake (g)	6.0 ± 10.2	4.6 ± 9.7	3.4 ± 8.0
Physical activity (h/week)	3.0 ± 2.4	2.7 ± 2.4	2.6 ± 2.2
Incident cases of myocardial infarction	1.4	6.3	4.0
Prevalent and incident cases of high blood pressure	25.2	35.9	50.4
Prevalent and incident cases of high cholesterol	25.0	29.4	34.0
Aspirin use	40.2	41.2	43.1
Current smoker	19.1	19.0	19.9
Postmenopausal	56.1	58.6	58.5
Postmenopausal hormone use	23.8	28.6	25.7

Data are means ± SD or %. *Values were calculated over person-time of the entire follow-up period and adjusted to the age distribution of the study population.

As described previously (24), thrombotic strokes were further classified as a large-artery occlusive infarction, lacunar infarction, or unclassified thrombotic infarction on the basis of CT scans, MRI, or autopsy, according to the criteria of the Perth Community Stroke Study (25). Interrater agreement of stroke subtypes in our cohort is high (24).

During 24 years of follow-up, 2,719 cases of a first nonfatal stroke were identified: 1,899 (69.8%) were confirmed by medical record review, and 820 (30.2%) were classified as probable, with 332 corroborated by letter and 488 by telephone. Stroke deaths were detected through information provided by the next of kin or postal authorities or by systematic searches of the National Death Index and documented by medical records and death certificates. Classification of fatal stroke was confirmed by review of hospital records, autopsy, or death certificate. If information was limited to death certificate or that provided by next of kin and no medical records were available, cases were classified as probable. Of 744 fatal strokes, 455 (61.2%) were confirmed by medical records and 289 (38.8%) were classified as probable, with 255 corroborated by telephone information provided by next of kin and 34 solely by death certificate. Of 3,463 total strokes, 2,354 (68%) were confirmed on the basis of medical records and 1,109 (32%) were classified as probable on the basis of supporting information. Results were comparable for the confirmed and probable cases; thus, confirmed and probable cases were combined for total stroke analyses. For analysis of specific stroke subtypes, only confirmed cases were included.

Ascertainment of diabetes

Cases of diabetes were identified from baseline and biennial follow-up questionnaires. When women reported a diagnosis of diabetes, a supplementary questionnaire was sent to ascertain diagnostic tests, treatments, and complications. Confirmation criteria conformed to guidelines of the National Diabetes Data Group (26) until 1997, when the revised criteria of the American Diabetes Association were implemented (27). In a substudy, 98.4% of our nurse participants' reports of type 2 diabetes were confirmed by medical records (28). Only women with definite type 1 or type 2 diabetes, based on the supplementary questionnaire, were considered in this analysis. We estimated duration of clinical diabetes by subtracting the date of diagnosis from the date of last completed questionnaire. Using the baseline questionnaire, we classified women as having type 1 diabetes if diabetes was first diagnosed at ≤30 years of age or they were currently using insulin and were ketosis prone (n = 303). Women in whom diabetes was first diagnosed at 30 years of age were classified as having type 2 diabetes (n = 10,766); 9,416 of these cases of diabetes were diagnosed during follow-up after 1976.

Covariates

Information on age, body weight, smoking status, weight change, aspirin use, alcohol intake, diet, lifestyle, family and personal medical history, and postmenopausal hormone therapy was collected at baseline or through the biennial questionnaires. We calculated BMI as the ratio of weight (in kilograms) to the square of height (in meters) (29). Waist and hip circumferences were self-reported in 1986 and 1996 (30), and physical activity was assessed in 1986, 1988, 1992, 1994, 1996, 1998, and 2000 (31). History of hypertension and hypercholesterolemia was self-reported with high validity (32).

We excluded from analysis women who reported type 2 diabetes that was not confirmed, whose date of diagnosis of diabetes was missing, or who reported diabetes onset at age <30 years but who were not taking insulin (n = 1,952) and whose date of birth was missing (n = 123), who died shortly after agreeing to participate in the study (n = 3), or who at baseline reported having cancer (n = 3,285) or stroke (n = 22). We thus included 116,316 women with a mean ± SD age of 54.0 ± 10.2 years.

Statistical analysis

We calculated incidence rates (cases of stroke per 100,000 person-years) from completion of the baseline questionnaire until the occurrence of stroke, date of the last completed questionnaire, death, or 1 June 2002, whichever came first. We estimated RRs using incidence rates (age adjusted), and hazard ratios (multivariate) from the Cox proportional hazards model with the SAS computer package (version 9.0; SAS Institute, Cary, NC). We considered as covariates BMI, menopausal status and use of postmenopausal hormones, smoking, physical activity, history of hypertension and hypercholesterolemia, ischemic heart disease that occurred during the follow-up, and use of aspirin and alcohol. To clarify the role of hypertension further, we also included the interaction terms of hypertension with type 2 diabetes in the "full" model. All tests for statistical significance were two tailed and performed at $\alpha < 0.05$.

RESULTS — Our analysis included 105,247 (90.5%) women without diabe-

Table 2—*Incidence rates and RRs of stroke subtypes by diabetes, the Nurses' Health Study, 1976–2002*

Variables	No diabetes	Type 1 diabetes	Type 2 diabetes
Total stroke			
Cases	2,384	33	637
Incidence*	92	475	240
Age-adjusted RR	1.0	5.9 (4.2–8.3)	2.3 (2.1–2.6)
Age- and hypertension-adjusted RR	1.0	5.3 (3.7–7.4)	1.9 (1.7–2.1)
Multivariate-adjusted RR†	1.0	4.7 (3.3–6.6)	1.8 (1.7–2.0)
Ischemic stroke			
Cases	1,083	20	373
Incidence*	42	288	140
Age-adjusted RR	1.0	7.9 (5.1–12.2)	3.0 (2.6–3.4)
Age- and hypertension-adjusted RR	1.0	7.0 (4.5–10.9)	2.4 (2.1–2.7)
Multivariate-adjusted RR†	1.0	6.3 (4.0–9.8)	2.3 (2.0–2.6)
Thrombotic stroke			
Cases	847	16	313
Incidence*	33	230	118
Age-adjusted RR	1.0	8.0 (4.9–13.1)	3.2 (2.8–3.6)
Age- and hypertension-adjusted RR	1.0	7.0 (4.3–11.5)	2.5 (2.2–2.9)
Multivariate-adjusted RR†	1.0	6.4 (3.9–10.5)	2.4 (2.1–2.7)
Large-artery occlusive infarction			
Cases	307	6	95
Incidence*	12	86	36
Age-adjusted RR	1.0	8.3 (3.7–18.7)	2.7 (2.2–3.4)
Age- and hypertension-adjusted RR	1.0	7.6 (3.4–17.1)	2.3 (1.8–2.9)
Multivariate-adjusted RR†	1.0	7.2 (3.2–16.2)	2.0 (1.6–2.6)
Lacunar infarction			
Cases	325	6	132
Incidence*	13	86	50
Age-adjusted RR	1.0	8.2 (3.7–18.4)	3.6 (2.9–4.4)
Age- and hypertension-adjusted RR	1.0	7.4 (3.3–16.5)	2.8 (2.3–3.5)
Multivariate-adjusted RR†	1.0	7.2 (3.2–16.1)	2.8 (2.3–3.5)
Hemorrhagic stroke			
Cases	257	3	31
Incidence*	10	43	12
Age-adjusted RR	1.0	4.5 (1.4–14.1)	1.1 (0.8–1.6)
Age- and hypertension-adjusted RR	1.0	4.3 (1.4–13.4)	1.0 (0.7–1.4)
Multivariate-adjusted RR†	1.0	3.8 (1.2–11.8)	1.0 (0.7–1.4)
Stroke of unknown subtype			
Cases	215	4	88
Incidence*	8	58	33
Age-adjusted RR	1.0	7.1 (2.6–19.1)	3.4 (2.6–4.3)
Age- and hypertension-adjusted RR	1.0	5.9 (2.2–15.9)	2.5 (1.9–3.2)
Multivariate-adjusted RR†	1.0	4.7 (1.7–12.7)	2.3 (1.7–3.0)

Data are *n* or RR (95% CI). *Incidence per 100,000 person-years. †Values were calculated by Cox proportional hazards model adjusted for age, BMI, physical activity, menopausal status and estrogen use, smoking and hypertension, high cholesterol, ischemic heart disease, aspirin use, and alcohol consumption.

tes, 303 (0.3%) with type 1 diabetes, and 10,766 (9.2%) with type 2 diabetes. Women with type 2 diabetes were older, had higher current BMI, BMI at age 18, and weight gain, and were less likely to drink alcohol than those without diabetes (Table 1). Women with either type of diabetes were more likely to have hypertension, hypercholesterolemia, and ischemic heart disease. The mean ± SD age of stroke was 67.8 ± 8.3 years for nondiabetic women, 63.4 ± 8.0 years for type 1 diabetic women, and 67.6 ± 7.3 years for type 2 diabetic women.

During 2.87 million person-years of follow-up, 3,463 (3.0%) incident cases of first stroke occurred, of which 744 were fatal. The overall incidence of stroke was 106 (95% CI 103–110) per 100,000 person-years. Of the 303 women who had type 1 diabetes, 33 subsequently had a stroke (475/100,000 person-years), an incidence higher than that for women with type 2 diabetes (240/100,000 person-years) (Table 2).

The risk of total stroke was sixfold higher in women with type 1 (RR 5.9 [95% CI 4.2–8.3]) and twofold higher among women with type 2 diabetes (2.3 [2.1–2.6]) than for nondiabetic women in age-adjusted models. The age-adjusted RR of thrombotic stroke was eightfold higher (8.0 [4.9–13.1]) in type 1 and threefold higher (3.2 [2.8–3.6]) in type 2 diabetes. Type 1 diabetes was also significantly associated with the age-adjusted risk of hemorrhagic stroke (4.5 [1.4–14.1]), but type 2 diabetes was not (1.1 [0.8–1.6]). Controlling for hypertension modestly attenuated these relationships, but additional adjustment for other time-dependent covariates did not appreciably alter the relationship between either type of diabetes and risk of stroke subtypes (Table 2). Ischemic stroke, lacunar infarction, and large-artery occlusive infarction had similar associations with diabetes. Women with longer duration of type 1 (data not shown) and type 2 diabetes (Table 3) tended to have a higher risk of stroke than did women with a shorter duration.

The association between type 2 diabetes and risk of ischemic stroke subtypes was seen in obese (BMI ≥30) and nonobese (BMI <30) women (Table 4). Likewise, the association between type 2 diabetes and risk of stroke subtypes was observed in both hypertensive and nonhypertensive women. The interaction terms of hypertension and diabetes for incidence of total stroke and stroke subtypes were not statistically significant.

CONCLUSIONS — In this 24-year follow-up study, both type 1 and type 2 diabetes were associated with a significantly higher risk of stroke and its subtypes in women, but the association with type 1 diabetes was stronger. The excess risk of stroke and its subtypes associated with type 2 diabetes was amplified in the presence of hypertension. We were not able to examine the relationship between diabetes and risk of subarachnoid or intraparenchymal hemorrhage because of the small number of cases.

The risk of stroke in patients with type 1 diabetes has been assessed in few epidemiological studies and usually with limited sample size, and the results have been inconsistent. In a multinational study, increased risk of stroke mortality was observed among individuals with type 1 and type 2 diabetes, but there was considerable variation among countries (19,20). A U.K. cohort study found higher total but not hemorrhagic stroke mortality among type 1 diabetic individuals than among the general population (18). Recently, a U.K. cohort study

Table 3—*Incidence rates and RRs of stroke subtypes by type 2 diabetes duration, the Nurses' Health Study, 1976–2002*

Variables	No diabetes	Duration of type 2 diabetes				
		<5 years	5–9 years	10–14 years	15–19 years	≥20 years
Total stroke						
Cases	2,384	78	89	126	125	211
Incidence*	92	109	155	292	360	429
Age-adjusted RR	1.0	1.2 (0.9–1.4)	1.5 (1.3–1.9)	2.7 (2.3–3.3)	3.3 (2.8–3.9)	3.9 (3.4–4.5)
Multivariate-adjusted RR†	1.0	1.1 (0.9–1.3)	1.4 (1.1–1.8)	2.4 (2.0–2.9)	2.9 (2.4–3.5)	3.3 (2.9–3.8)
Ischemic stroke						
Cases	1,083	50	50	67	77	125
Incidence*	42	70	87	156	222	254
Age-adjusted RR	1.0	1.6 (1.2–2.2)	1.9 (1.4–2.5)	3.1 (2.4–4.0)	4.4 (3.5–5.5)	4.9 (4.1–5.9)
Multivariate-adjusted RR†	1.0	1.5 (1.1–2.0)	1.7 (1.3–2.3)	2.8 (2.1–3.6)	3.8 (3.0–4.8)	4.1 (3.4–5.0)
Thrombotic stroke						
Cases	847	41	41	51	66	111
Incidence*	33	57	71	118	190	226
Age-adjusted RR	1.0	1.7 (1.3–2.4)	2.0 (1.5–2.7)	3.0 (2.3–4.0)	4.8 (3.7–6.2)	5.6 (4.6–6.8)
Multivariate-adjusted RR†	1.0	1.5 (1.1–2.1)	1.8 (1.3–2.4)	2.6 (1.9–3.5)	4.0 (3.1–5.2)	4.5 (3.7–5.6)
Large-artery occlusive infarction						
Cases	307	18	13	13	25	25
Incidence*	12	25	23	30	72	51
Age-adjusted RR	1.0	2.1 (1.3–3.3)	1.8 (1.01–3.1)	2.2 (1.3–3.8)	5.2 (3.4–7.8)	3.6 (2.4–5.5)
Multivariate-adjusted RR†	1.0	1.7 (1.1–2.8)	1.5 (0.8–2.6)	1.8 (1.04–3.2)	4.3 (2.8–6.5)	2.9 (1.9–4.4)
Lacunar infarction						
Cases	325	15	20	26	25	45
Incidence*	13	21	35	60	72	92
Age-adjusted RR	1.0	1.6 (0.9–2.7)	2.5 (1.6–3.9)	4.1 (2.7–6.1)	4.9 (3.3–7.4)	6.3 (4.6–8.7)
Multivariate-adjusted RR†	1.0	1.5 (0.9–2.5)	2.3 (1.5–3.7)	3.7 (2.5–5.6)	4.5 (3.0–6.9)	5.6 (4.1–7.8)
Hemorrhagic stroke						
Cases	257	7	7	9	3	5
Incidence*	10	10	12	21	9	10
Age-adjusted RR	1.0	1.0 (0.5–2.1)	1.2 (0.6–2.5)	1.9 (1.0–3.7)	0.8 (0.3–2.5)	0.9 (0.4–2.2)
Multivariate-adjusted RR†	1.0	0.9 (0.4–2.0)	1.1 (0.5–2.4)	1.8 (0.9–3.6)	0.7 (0.2–2.3)	0.9 (0.2–2.1)

Data are *n* or RR (95% CI). *Incidence per 100,000 person-years. †Values calculated by Cox proportional hazards model adjusted for age, BMI, physical activity, menopausal status and estrogen use, smoking and hypertension, high cholesterol, ischemic heart disease, aspirin use, and alcohol consumption.

showed that total stroke mortality was 4.8-fold higher in women with type 1 diabetes than in nondiabetic women (33). Our study suggests that type 1 diabetes markedly raises the risk of all stroke subtypes in women. Women with type 1 diabetes have a 6.3-fold higher risk of ischemic stroke, a nearly fourfold higher risk of hemorrhagic stroke, and a sevenfold higher risk of large-artery occlusive and lacunar infarction than women without diabetes, even after controlling for

Table 4—*RRs of stroke subtypes and diabetes, according to hypertension and obesity status, the Nurses' Health Study, 1976–2002*

Variables	Hypertension				Obesity		
	No diabetes and no hypertension	No diabetes and hypertension	Diabetes and no hypertension	Diabetes and hypertension	No diabetes and BMI <30 kg/m^2	Diabetes and BMI <30 kg/m^2	Diabetes and BMI ≥30 kg/m^2
Total stroke							
Cases	1,065	1,319	136	501	1,931	354	267
Incidence*	54	207	106	365	86	236	238
RR†	1.0	2.3 (2.1–2.5)	1.9 (1.6–2.3)	4.1 (3.6–4.6)	1.0	1.8 (1.6–2.0)	1.9 (1.6- 2.3)
Ischemic stroke							
Cases	458	625	80	293	887	201	161
Incidence*	23	98	62	213	40	134	144
RR†	1.0	2.3 (2.0–2.6)	2.5 (2.0–3.2)	5.1 (4.3–6.0)	1.0	2.1 (1.8–2.5)	2.0 (1.6- 2.6)
Hemorrhagic stroke							
Cases	157	100	9	22	219	20	11
Incidence*	8	16	7	16	10	13	10
RR†	1.0	1.6 (1.2–2.1)	0.9 (0.4–1.7)	1.6 (1.0–2.6)	1.0	1.1 (0.7–1.8)	1.3 (0.6–2.8)

Data are *n* or RR (95% CI). *Incidence per 100,000 person-years. †RRs (with 95% CI) calculated by Cox proportional hazards model adjusted for age, BMI, physical activity, menopausal status and estrogen use, smoking and hypertension, high cholesterol, ischemic heart disease, aspirin use, and alcohol consumption.

age, BMI, and other cardiovascular risk factors.

Most studies have shown that type 2 diabetes is an important risk factor for ischemic stroke, whereas the incidence of hemorrhagic stroke has not been increased (16,17,34) or has been significantly decreased (1). We found an increased risk of hemorrhagic stroke among women with type 1 diabetes; however, this result was based on only three cases. Although there was no significant risk for those with type 2 diabetes, our results could not exclude a 40–60% increased risk for hemorrhagic stroke. In the Rochester, Minnesota, study (15), type 2 diabetes was not an independent risk factor for stroke among women. In the joint report from the Honolulu Heart Study and the Framingham Stroke Study, the incidence of ischemic stroke was more than twofold higher in patients with diabetes than in the general population, whereas the rates of hemorrhagic stroke were almost the same (2). In the Asia Pacific Cohort Studies, ischemic stroke was increased 2.6-fold, whereas hemorrhagic stroke was not significantly increased (35). In the Honolulu Heart Program, diabetes was not associated with an increased risk of hemorrhagic stroke in men, whereas in the Framingham Study, there was a 4.5-fold higher risk of hemorrhagic stroke in men with diabetes (3). For hemorrhagic stroke, a study showed that in patients with both diabetes and arterial hypertension, the severity of fibrinoid necrosis of small cerebral arteriole walls, often associated with intracerebral hemorrhage, was less pronounced than in those with hypertension alone (36).

Our findings of an excess of lacunar infarcts in women with diabetes have been observed in other studies (37,38). Diabetes can cause small-vessel arteriolopathy, especially in the retina, kidney, and deep structures in the brain (39).

The pathophysiology of cerebrovascular disease in patients with diabetes is not fully characterized, but both large and small blood vessels seem to be affected. Potential underlying mechanisms include excess glycation, endothelial dysfunction, increased platelet aggregation, impaired fibrinolysis, and insulin resistance. Associated dyslipidemia and hypertension also probably contribute (40). Endothelial proliferation and thickening of the basement membrane in small blood vessels lead to increased risk of lacunar infarction (41,42). Increased coagulability and platelet aggregability as well as decreased fibrinolysis in diabetic patients may augment the risk of large-artery infarction (40). To decrease the risk of stroke associated with diabetes, treatment of underlying glycemia, hypertension, dyslipidemia, and platelet aggregation must all be considered.

We found that the incidence of stroke subtypes was higher in women with type 1 diabetes than in women with type 2 diabetes. A higher incidence of stroke subtypes among those with type 1 diabetes could be attributable to younger age at onset, longer duration of diabetes, insulin deficiency, and development of hypertension with diabetic nephropathy, disturbances of coagulation-fibrinolytic parameters, increased platelet adhesiveness, or episodes of hypoglycemia. This finding warrants further study.

Obesity is associated with both type 2 diabetes and stroke. A Japanese study (8) showed that the excess risk of ischemic stroke associated with diabetes was observed primarily in nonhypertensive subjects and in those with high BMI. However, we found that type 2 diabetes was associated with increased risk for ischemic stroke subtypes regardless of obesity. Similarly, our findings confirm those of other studies (5,11,19,43) that the risk of stroke associated with a history of both type 2 diabetes and hypertension was substantially greater than that for diabetes alone.

Our study has several strengths and limitations. The strengths include the prospective cohort design, long-term follow-up, large sample size, and detailed information on potential confounding factors. Data collection on incident strokes was quite complete, and a high percentage of events was confirmed by imaging studies. Selection and information bias was unlikely because of the prospective design and high rate of follow-up.

One limitation of our study was that because diabetes was determined by self-report and confirmed through a validated diagnostic questionnaire, those participants identified as not having diabetes inevitably included some women with undiagnosed type 2 diabetes. However, this misclassification would tend to reduce rather than increase the significance of differences between diabetes and stroke. A few women with type 2 diabetes may have been misclassified as having type 1 diabetes, and some with late onset type 1 diabetes may have been included in our group of women with type 2 diabetes; however, these misclassifications are unlikely to have accounted for the observed differences in risk. Although residual confounding may be present owing to imperfect measurement of dietary components and lipid levels, it is unlikely to account for more than a portion of the remaining excess risk. Additionally, because the study participants were mainly white women, the results may not apply to other racial/ethnic groups or to men.

In summary, our study indicates that women with both type 1 and type 2 diabetes have an increased risk for ischemic stroke and that type 1 diabetes is associated with excess risk of hemorrhagic stroke. The risk of stroke is also associated with duration of type 2 diabetes. With the worldwide increasing prevalence of diabetes, the population-attributable risk of stroke will probably increase. Our results also emphasize the importance of controlling all known stroke risk factors, especially hypertension, in patients with diabetes.

Acknowledgments— National Institutes of Health Grants DK58845, HL34594, and P01CA87969 supported this work.

References

1. Jorgensen H, Nakayama H, Raaschou HO, Olsen TS: Stroke in patients with diabetes: the Copenhagen Stroke Study. *Stroke* 25:1977–1984, 1994
2. Rodriguez BL, D'Agostino R, Abbott RD, Kagan A, Burchfiel CM, Yano K, Ross GW, Silbershatz H, Higgins MW, Popper J, Wolf PA, Curb JD: Risk of hospitalized stroke in men enrolled in the Honolulu Heart Program and the Framingham Study: a comparison of incidence and risk factor effects. *Stroke* 33:230–236, 2002
3. D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB: Stroke risk profile: adjustment for antihypertensive medication: the Framingham Study. *Stroke* 25:40–43, 1994
4. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, Arky RA, Speizer FE, Hennekens CH: A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med* 151:1141–1147, 1991
5. Kissela BM, Khoury J, Kleindorfer D, Woo D, Schneider A, Alwell K, Miller R, Ewing I, Moomaw CJ, Szarflaski JP, Ebel J, Shukla R, Broderick JP: Epidemiology of ischemic stroke in patients with diabetes: the greater Cincinnati/Northern Kentucky Stroke Study. *Diabetes Care* 28: 355–359, 2005
6. Folsom AR, Rasmussen ML, Chambless LE Howard G, Cooper LS, Schmidt MI, Heiss G: Prospective associations of fast-

ing insulin, body fat distribution, and diabetes with risk of ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study investigators. *Diabetes Care* 22:1077–1083, 1999
7. Lehto S, Ronnemaa T, Pyorala K, Laakso M: Predictors of stroke in middle-aged patients with non-insulin-dependent diabetes. *Stroke* 27:63–68, 1996
8. Iso H, Imano H, Kitamura A, Sato S, Naito Y, Tanigawa T, Ohira T, Yamagishi K, Iida M, Shimamoto T: Type 2 diabetes and risk of non-embolic ischemic stroke in Japanese men and women. *Diabetologia* 47: 2137–2144, 2004
9. Lawes CM, Parag V, Bennett DA, Suh I, Lam TH, Whitlock G, Barzi F, Woodward M; Asia Pacific Cohort Studies Collaboration: Blood glucose and risk of cardiovascular disease in the Asia Pacific region. *Diabetes Care* 27:2836–2842, 2004
10. Almdal T, Scharling H, Jensen JS, Vestergaard H: The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. *Arch Intern Med* 164:1422–1426, 2004
11. Davis TM, Millns H, Stratton IM, Holman RR, Turner RC: Risk factors for stroke in type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS). *Arch Intern Med* 159:1097–1103, 1999
12. Haheim LL, Holme I, Hjermann I, Leren P: Risk factors of stroke incidence and mortality: a 12-year follow-up of the Oslo Study. *Stroke* 24:1484–1489, 1993
13. Carrieri PB, Orefice G, Maiorino A, Provitera V, Balzano G, Lucariello A: Age-related risk factors for ischemic stroke in Italian men. *Neuroepidemiology* 13: 28–33, 1994
14. Simons LA, McCallum J, Friedlander Y, Simons J: Risk factors for ischemic stroke: Dubbo Study of the elderly. *Stroke* 29:1341–1346, 1998
15. Davis PH, Dambrosia JM, Schoenberg BS, Schoenberg DG, Pritchard DA, Lilienfeld AM, Whisnant JP: Risk factors for ischemic stroke: a prospective study in Rochester, Minnesota. *Ann Neurol* 22:319–327, 1987
16. Knekt P, Reunanen A, Aho K, Heliovaara M, Rissanen A, Aromaa A, Impivaara O: Risk factors for subarachnoid hemorrhage in a longitudinal population study. *J Clin Epidemiol* 44:933–939, 1991
17. Megherbi SE, Milan C, Minier D, Couvreur G, Osseby GV, Tilling K, Di Carlo A, Inzitari D, Wolfe CD, Moreau T, Giroud M; European BIOMED Study of Stroke Care Group: Association between diabetes and stroke subtype on survival and functional outcome 3 months after stroke: data from the European BIOMED Stroke Project. *Stroke* 344:688–694, 2003
18. Laing SP, Swerdlow AJ, Carpenter LM, Slater SD, Burden AC, Botha JL, Morris AD, Waygh NR, Gatling W, Gale EA, Patterson CC, Qiao Z, Keen H: Mortality from cerebrovascular disease in a cohort of 23 000 patients with insulin-treated diabetes. *Stroke* 34:418–421, 2003
19. Fuller JH, Stevens LK, Wang SL: Risk factors for cardiovascular mortality and morbidity: the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 44 (Suppl. 2):S54–S64, 2001
20. Fuller JH, Stevens LK, Wang SL: International variations in cardiovascular mortality associated with diabetes mellitus: the WHO Multinational Study of Vascular Disease in Diabetes. *Ann Med* 28:319–322, 1996
21. Deckert T, Poulsen JE, Larsen M: Prognosis of diabetics with diabetes onset before the age of thirty-one. *Diabetologia* 14: 363–370, 1978
22. Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, Hennekens CH: Test of the National Death Index. *Am J Epidemiol* 119:837–839, 1984
23. Walker AE, Robins M, Weinfeld FD: The National Survey of Stroke: clinical findings. *Stroke* 12 (Suppl. 1):113–144, 1981
24. Iso H, Rexrode K, Hennekens CH, Manson JE: Application of computer tomography-oriented criteria for stroke subtype classification in a prospective study. *Ann Epidemiol* 10:81–87, 2000
25. Anderson CS, Jamrozik KD, Burvill PW, Chakera TMH, Johnson GA, Stewart-Wynne EG: Determining the incidence of different subtypes of stroke: results from the Perth Community Stroke Study, 1989–1990. *Med J Aust* 158:85–89, 1993
26. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–1057, 1979
27. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 23(Suppl. 1):S4–S19, 2000
28. Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS, Rosner B, Hennekens CH, Speizer FE: Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 338:774–778, 1991
29. Willett W, Stampfer MJ, Bain C, Lipnick R, Speizer FE, Rosner B, Cramer D, Hennekens CH: Cigarette smoking, relative weight, and menopause. *Am J Epidemiol* 117:651–658, 1983
30. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC: Validity of self-reported waist and hip circumferences in men and women. *Epidemiology* 1:466–473, 1990
31. Wolf AM, Hunter DJ, Colditz GA, Manson JE, Stampfer MJ, Corsano KA, Rosner B, Kriska A, Willett WC: Reproducibility and validity of a self-administered physical activity questionnaire. *Int J Epidemiol* 23:991–999, 1994
32. Colditz GA, Martin P, Stampfer MJ, Willett WC, Sampson L, Rosner B, Hennekens CH, Speizer FE: Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol* 123: 894–900, 1986
33. Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM: High risk of cardiovascular disease in patients with type 1 diabetes in the U.K.: a cohort study using the general practice research database. *Diabetes Care* 29:798–804, 2006
34. Hu G, Sarti C, Jousilahti P, Peltonen M, Qiao O, Antikainen R, Tuomilehto J: The impact of history of hypertension and type 2 diabetes at baseline on the incidence of stroke and stroke mortality. *Stroke* 36:2538–2543, 2005
35. Asia Pacific Cohort Studies Collaboration: The effects of diabetes on the risk of major cardiovascular diseases and death in the Asia-Pacific region. *Diabetes Care* 26: 360–366, 2003
36. Aronson SM: Intracranial vascular lesions in patients with diabetes mellitus. *J Neuropathol Exp Neurol* 32:183–196, 1973
37. Arboix A, Rivas A, Garcia-Eroles L, de Marcos L, Massons J, Oliveres M: Cerebral infarction in diabetes: clinical pattern, stroke subtypes, and predictors of in-hospital mortality. *BMC Neurol* 5:9, 2005
38. Arboix A, Morcillo C, García-Eroles L, Massons J, Oliveres M, Targa C: Different vascular risk factor profiles in ischemic stroke subtypes. *Acta Neurol Scand* 102: 264–270, 2000
39. Fisher CM: Lacunar infarcts: a review. *Cerebrovasc Dis* 1:311–320, 1991
40. Beckman JA, Creager MA, Libby P: Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 287:2570–2581, 2002
41. Monkovsky BN, Ziegler D: Stroke in patients with diabetes mellitus. *Diabetes Metab Res Rev* 20:268–287, 2004
42. Idris I, Thomson GA, Sharma JC: Diabetes mellitus and stroke. *Int J Clin Pract* 60:48–56, 2006
43. Karapanayiotides T, Piechowski-Jozwiak B, van Melle G, Bogousslavsky J, Devuyst G: Stroke patterns, etiology, and prognosis in patients with diabetes mellitus. *Neurology* 62:1558–1562, 2004