

Duration of Diabetes and Risk of Ischemic Stroke

The Northern Manhattan Study

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Background and Purpose—Diabetes increases stroke risk, but whether diabetes status immediately before stroke improves prediction and whether duration is important are less clear. We hypothesized that diabetes duration independently predicts ischemic stroke.

Methods—Among 3298 stroke-free participants in the Northern Manhattan Study, baseline diabetes and age at diagnosis were determined. Incident diabetes was assessed annually (median, 9 years). Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% CI for incident ischemic stroke using baseline diabetes, diabetes as a time-dependent covariate, and duration of diabetes as a time-varying covariate; models were adjusted for demographic and cardiovascular risk factors.

Results—Mean age was 69 ± 10 years (52% Hispanic, 21% white, and 24% black); 22% had diabetes at baseline and 10% had development of diabetes. There were 244 ischemic strokes, and both baseline diabetes (HR, 2.5; 95% CI, 1.9–3.3) and diabetes considered as a time-dependent covariate (HR, 2.4; 95% CI, 1.8–3.2) were similarly associated with stroke risk. Duration of diabetes was associated with ischemic stroke (adjusted HR, 1.03 per year with diabetes; 95% CI, 1.02–1.04). Compared to nondiabetic participants, those with diabetes for 0 to 5 years (adjusted HR, 1.7; 95% CI, 1.1–2.7), 5 to 10 years (adjusted HR, 1.8; 95% CI, 1.1–3.0), and ≥ 10 years (adjusted HR, 3.2; 95% CI, 2.4–4.5) were at increased risk.

Conclusions—Duration of diabetes is independently associated with ischemic stroke risk adjusting for risk factors. The risk increases 3% each year, and triples with diabetes ≥ 10 years. (*Stroke*. 2012;43:1212-1217.)

Key Words: acute stroke ■ cerebral infarct ■ diabetes mellitus ■ epidemiology ■ risk factors

Diabetes mellitus is a major public health burden. In the United States, >23.6 million people have diabetes.¹ Prevalence is increasing as the population ages and certain populations, such as minority groups, are more vulnerable. The number of people with diabetes diagnosed is estimated to increase 165% between 2000 and 2050.² The independent association of diabetes with stroke is now well-documented.^{3–10} Notably, almost all prospective cohort studies have evaluated diabetes as an exposure at baseline, or the time of participant enrollment, and measured its effect on stroke outcomes during follow-up. In large cohorts with long periods of follow-up, a significant proportion of participants who did not have diabetes at baseline had development of diabetes over the period of follow-up.¹¹ Taking this change in status into consideration may be expected to provide a more precise estimate of stroke risk.

Although some studies have assessed the relationship of duration of diabetes to risk of cardiovascular outcomes

such as coronary heart disease, cardiovascular mortality, peripheral arterial disease, carotid wall thickness, and thin cap fibroatheroma,^{12–18} the association between duration of diabetes and stroke risk is less well-studied.

The Northern Manhattan Study prospective cohort, with its annual evaluation of diabetes diagnosis, provides an opportunity to investigate the utility of incorporating serial interval evaluations of diabetes into risk prediction estimates. We investigated the effect of updated diabetes status on stroke by incorporating diabetes as a time-dependent covariate. We further examined the effect of duration of diabetes on ischemic stroke risk.

Materials and Methods

Northern Manhattan Study is a prospective population-based cohort study designed to determine stroke incidence, risk factors, and prognosis in an urban multiethnic population. Northern Manhattan is defined as the area in New York City north of 145th Street, south of

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218th Street, bound on the west by the Hudson River, and separated from the Bronx on the east by the Harlem River. The cohort has a racial/ethnic mixture consisting of 52.3% Hispanic, 24.3% non-Hispanic black, and 20.9% non-Hispanic white residents.

Selection of Prospective Cohort

The study has been previously described in detail.^{19–22} Briefly, community participants were eligible for enrollment if they: (1) had never had a stroke diagnosed; (2) were 40 years of age or older; and (3) resided for ≥ 3 months in a household with a telephone in northern Manhattan. Subjects were identified with random digit dialing using dual-frame sampling to identify both published and unpublished phone numbers. The protocol was approved by the Institutional Review Board at Columbia University Medical Center and the Miller School of Medicine, University of Miami, and participants provided informed consent.

Baseline Evaluation

Baseline data were collected via interviews by trained research assistants, medical record review, physical and neurological examination by study investigators, in-person measurements, and collection of fasting blood specimens for glucose and lipid measurements. A standardized questionnaire was adapted from the Behavioral Risk Factor Surveillance System²³ developed by the Centers for Disease Control and Prevention regarding the following conditions: diabetes, hypertension, hypercholesterolemia, smoking, peripheral vascular disease, transient ischemic attack, and cardiac disease (including angina, myocardial infarction, coronary artery disease, atrial fibrillation, and valvular heart disease).

Interval Evaluation

All participants were prospectively followed-up annually through telephone interviews, and mean duration of follow-up at time of analysis was 9.0 ± 3.7 years. The yearly contact rate was 99%. Subjects were interviewed to determine changes in vital status, detect cardiac and neurological symptoms and events, and review any hospitalizations. The telephone assessment served as a screen for vascular events. The simple stroke question (“Since your last contact have you been diagnosed with a stroke?”) during telephone interview was 92% sensitive and 95% specific with in-person assessment, physician interviews, medical records, and neuroimaging data used as the gold standards.²¹ Participants with affirmative responses to neurological symptoms underwent examination and review by a study neurologist or had medical records reviewed. Hospital surveillance of admission and discharge were performed to provide data that may have been missed during the annual telephone follow-up.

Measure of Exposure

Diabetes at baseline was defined if a participant reported a history of medical diagnosis of diabetes mellitus or treatment with oral hypoglycemic agents or insulin. In addition, fasting blood glucose ≥ 126 mg/dL (6.5 mmol/L) was used among those who did not self-report diabetes to adjudicate diabetic status and find “unaware” cases. Fasting blood glucose was measured using a Hitachi 747 automated spectrometer (Boehringer). Age at time of diagnosis was also recorded for those with self-report of diabetes at baseline, and diabetes duration was calculated. During follow-up evaluations among nondiabetic participants, the first follow-up contact at which there was self-report of new diagnosis of diabetes, treatment with oral hypoglycemic drugs, or insulin therapy was used to define conversion to diabetes during follow-up. Duration of diabetes was calculated from the onset of diabetes up to the date of ischemic stroke or censoring.

Validation of Diabetes Status Determined During Follow-Up

There were 74 instances in which a participant reported treatment with antidiabetic drugs or insulin without ever reporting the diagnosis of diabetes. Medical records were reviewed to validate these responses. The self-report of medications or insulin without report of

the diagnosis of diabetes was consistent with a diagnosis of diabetes in 92% of cases. We reflected these changes in the analyses.

Similarly, there were 87 participants who self-reported the diagnosis of diabetes once but never reported any subsequent treatment. All these cases were confirmed to have diabetes on medical record review.

To avoid potential bias caused by intensive medical record review selectively among those with possible diabetes conversion during follow-up, and to validate the nonreport of diabetes diagnosis or treatment among the remainder of the cohort, medical record review of a random computer-generated list of 50 participants who never reported diabetes during follow-up was performed. Two participants had the diagnosis in the medical record but it had not been detected in interview that year. On further review, it was determined that these participants did not report the diagnosis because it was “diet-controlled diabetes” at that time, and they reported the diagnosis on subsequent follow-up once they started using medication.

Measurement of Outcome

Stroke was defined during follow-up by the first symptomatic occurrence of any type of stroke including intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral infarction, as previously described.¹⁹ Medical records were reviewed to verify details of suspected events. At least 2 neurologists reviewed data independently and classified strokes. Any disagreements were adjudicated by the principal investigators (R.L.S. and M.E.). We used only ischemic strokes for current analyses.

Statistical Analyses

All analyses were performed using SAS version 9.1 (SAS Institute). The distributions of diabetes at baseline were calculated, both overall and by subject characteristics, including demographics and risk factors. Cox proportional hazard regression models were fitted to calculate hazard ratios (HR) and 95% CI for ischemic stroke as the outcome. Main predictors were baseline diabetes, diabetes as time-varying covariate (incorporating new-onset diabetes during follow-up), and duration of diabetes as time-varying covariate. We used duration of diabetes as a continuous measure as well as categorized at 5 and 10 years to examine for threshold effects.

Models unadjusted and adjusted for demographic factors (age, sex, race–ethnicity, insurance status, and educational level) and behavioral and medical risk factors (hypertension, cardiac disease, high-density lipoprotein, low-density lipoprotein, current smoking, past smoking, alcohol consumption, waist circumference, and physical activity) were constructed. Assessment for 2-way interactions was conducted. We compared the Akaike Information Criterion among the baseline and the time-varying diabetes models.

Results

Baseline Characteristics

Baseline characteristics of the cohort are shown in Table 1. The mean age was 69 ± 10 years; 62.8% of the cohort were women, 52.3% were Hispanic, 20.9% were non-Hispanic white, and 24.3% were non-Hispanic black.

At baseline, 574 participants (17.4%) self-reported diabetes and 142 subjects had fasting blood glucose > 126 mg/dL, for a total of 716 (21.8%) with diabetes at baseline. Approximately 93% to 96% of participants visited their primary care physician at least once during the previous year for each year of follow-up. Among those who did not have diabetes at baseline ($n=2582$), 338 subjects (13.1%) reported new-onset diabetes during a mean 9.0 years of follow-up.

Diabetes at Baseline and as a Time-Dependent Covariate

There were 244 incident ischemic strokes. Baseline diabetes was associated with risk of stroke (unadjusted HR, 2.6; 95%

Table 1. Baseline Sociodemographic and Cardiovascular Risk Factors in the Northern Manhattan Study

Sociodemographic and Cardiovascular Risk Factors, N (%) or Mean \pm SD	Total	Diabetes at Enrollment	No Diabetes at Enrollment	Persistently Without Diabetes	New Diabetes During Follow-Up	P Value*
N	3298	716 (21.7%)	2582 (78.2%)	2244 (68.0%)	338 (10.2%)	
Age (y)	69 \pm 10	69 \pm 8	69 \pm 11	70 \pm 11	66 \pm 9	0.43
Sex						
Women	2071 (62.8%)	438 (61.2%)	1633 (63.2%)	1425 (63.5%)	208 (61.5%)	
Men	1227 (37.2%)	278 (38.8%)	949 (36.8%)	819 (36.5%)	130 (38.5%)	0.31
Race/ethnicity						
White	690 (20.9%)	100 (14.0%)	590 (22.9%)	556 (24.8%)	34 (10.1%)	Reference
Black	803 (24.3%)	196 (27.4%)	607 (23.5%)	552 (24.6%)	55 (16.3%)	<0.0001
Hispanic	1726 (52.3%)	408 (57.0%)	1318 (51.0%)	1076 (48.0%)	242 (71.6%)	<0.0001
Completed high school education	1511 (45.8%)	282 (39.4%)	1229 (47.6%)	1107 (49.3%)	122 (36.1%)	<0.0001
Insurance						
Medicaid/no insurance	1435 (43.5%)	375 (52.4%)	1060 (41.1%)	870 (38.8%)	190 (56.2%)	<0.0001
Medicare/private insurance	1841 (55.8%)	335 (46.8%)	1506 (58.3%)	1358 (60.5%)	148 (43.8%)	Reference
Smoking status						
None	1548 (46.9%)	317 (44.3%)	1231 (47.7%)	1076 (48.0%)	155 (45.9%)	Reference
Past	1179 (35.7%)	273 (38.1%)	906 (35.1%)	787 (35.1%)	119 (35.2%)	0.09
Current	569 (17.3%)	126 (17.6%)	443 (17.2%)	379 (16.9%)	64 (18.9%)	0.42
Moderate alcohol consumption	1075 (32.6%)	181 (25.3%)	894 (34.6%)	796 (35.5%)	98 (29.0%)	<0.0001
Any physical activity	1909 (57.9%)	380 (53.1%)	1529 (59.2%)	1352 (60.2%)	177 (52.4%)	0.0027
Cardiac disease	792 (24.0%)	210 (29.3%)	582 (22.5%)	500 (22.3%)	82 (24.3%)	0.0002
Waist circumference (in)	36.8 \pm 5.0	38.4 \pm 5.0	36.3 \pm 4.9	36 \pm 5.0	38.4 \pm 4.6	<0.0001
High-density lipoprotein (mg/dL)	46.8 \pm 14.6	43.7 \pm 14.0	47.6 \pm 14.6	48.4 \pm 14.7	42.7 \pm 13.3	<0.0001
Low-density lipoprotein (mg/dL)	129.1 \pm 36.1	126.3 \pm 39.1	130.0 \pm 35.3	129.8 \pm 35.3	130.8 \pm 35.0	0.02
Systolic blood pressure (mm Hg)	143.7 \pm 21.0	146.7 \pm 20.0	142.9 \pm 21.3	142.7 \pm 21.2	144.2 \pm 22.0	<0.0001

SD indicates standard deviation.

*Diabetes at baseline vs no diabetes at baseline.

CI, 2.0–3.3). In the fully adjusted model, adjusted for demographic and other cardiovascular risk factors including smoking, alcohol consumption, low-density lipoprotein, high-density lipoprotein, blood pressure, waist circumference, history of cardiac disease, and physical activity, the association was unchanged (adjusted HR, 2.5; 95% CI, 1.9–3.3; Table 2). When new-onset diabetes was taken into account as a time-varying covariate, diabetes was still associated with risk of ischemic stroke (adjusted HR, 2.4; 95% CI, 1.8–3.2). The Akaike Information Criteria for the models were similar (3333.1 for the model using baseline diabetes and 3335.2 in the model using diabetes as a time-dependent covariate). There were no interactions between diabetes and age, race—ethnicity, or sex.

Duration of Diabetes

The mean duration of diabetes among people who self-reported diabetes at baseline was 17.3 \pm 11.6 years (median, 13.7 years). Among the 338 subjects with diabetes diagnosed during follow-up, mean duration was 4.5 \pm 3.2 years (median, 4.2 years). With each year of diabetes, stroke risk increased by 3% (adjusted HR per year, 1.03; 95% CI, 1.02–1.04).

Duration was also categorized as <5 years, 5 to 10 years, and \geq 10 years, with nondiabetic participants as a reference

group. Without assuming linearity, the trichotomized duration of diabetes variable was fitted adjusting for other risk factors. The null hypothesis that all 3 groups had the same risk of stroke was rejected (χ^2 test with 2 degrees of freedom, $P=0.01$). Compared to those without diabetes, those with

Table 2. Risk of Ischemic Stroke Associated With Baseline Diabetes and Diabetes as Time-Dependent Covariate

Models	Hazard Ratio	95% Confidence Interval
Baseline diabetes		
Unadjusted (diabetes only)	2.6	2.0–3.3
Adjusted for demographic variables*	2.7	2.1–3.5
Adjusted for demographic variables and cardiovascular risk factors†	2.5	1.9–3.3
Diabetes as time-dependent covariate		
Unadjusted (diabetes only)	2.5	1.9–3.2
Adjusted for demographic variables*	2.6	2.0–3.4
Adjusted for demographic variables and cardiovascular risk factors†	2.4	1.8–3.2

*Age, sex, education, race—ethnicity, and insurance.

†Age, sex, education, race—ethnicity, insurance, waist circumference, alcohol consumption, smoking status, physical activity, high-density lipoprotein, low-density lipoprotein, history of cardiac disease, and systolic blood pressure.

Table 3. Risk of Ischemic Stroke Associated With Duration of Diabetes

Diabetes Duration	Hazard Ratio*	95% Confidence Interval	P Value
Continuous model			
Per year	1.03	1.02–1.04	<0.0001
Categorical model†			
≤5 y	1.72	1.09–2.71	.02
5–10 y	1.83	1.13–2.97	.01
≥10 y	3.23	2.36–4.51	<0.0001

*Adjusted for age, sex, race–ethnicity, education, insurance, waist circumference, smoking status, alcohol consumption, physical activity, systolic blood pressure, history of cardiac disease, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol.

†Participants without diabetes as reference group.

diabetes <5 years (adjusted HR, 1.7; 95% CI, 1.1–2.7), 5 to 10 years (adjusted HR, 1.8; 95% CI, 1.1–3.0), and ≥10 years (adjusted HR, 3.2; 95% CI, 2.4–4.5) had an increased risk of stroke (Table 3 and Figure).

Discussion

In this prospective cohort, diabetes at time of enrollment was associated with ischemic stroke risk, consistent with estimates of association reported in other studies, varying from 1.3 to 4.0.^{3–10,24} Contrary to our hypothesis, however, the magnitude of the association for diabetes with stroke risk was no different when we included diabetes as a time-dependent covariate. In traditional epidemiological analyses, the use of only baseline assessments of a risk factor, such as diabetes, could potentially bias study results toward the null. Our findings suggest that there is marginal incremental value to including further assessments of diabetes during follow-up in analyses of its effect on stroke risk. One practical implication for future epidemiological studies would be potential cost-savings through avoiding additional lengthy interviews and assessments of risk factors during follow-up. Whether these findings are transferable to other risk factors and cardiovascular outcomes is not clear from these analyses.

There are several possible explanations for this absence of additional information from follow-up assessments in our analyses. The cardiovascular risk factor burden carried by the participants at enrollment (mean age, 69 years) could already be high enough that development of diabetes during

follow-up does not confer added information. Second, subjects with newly diagnosed diabetes may be more compliant with treatment, which has been shown to be beneficial for primary stroke prevention in our cohort.²⁵ Third, the median duration of follow-up for those with diabetes at baseline in our cohort was 13.7 years, but it was only 4.2 years for those with development of diabetes after baseline, which may not be sufficient to manifest cerebrovascular events. Last, we used both self-report and laboratory results to identify diabetes at baseline. However, self-report alone was used to define diabetes during telephone follow-up, which may have led us to miss cases, because nearly one-third of diabetes cases may be undiagnosed.²⁶

Among those with diabetes ≥10 years, risk of ischemic stroke is 3-times the risk among those without diabetes. Our study provides evidence that the risk of ischemic stroke increased continuously with duration of diabetes mellitus. The increase is not as much during the second half of the first decade, but it increases steeply as the disease enters its second decade. This must, however, be interpreted keeping in mind that true onset of diabetes may be 4 to 7 years earlier than clinical diagnosis.²⁷

This is the first prospective cohort study to address the association of diabetes duration and ischemic stroke among both men and women. The Nurses' Health study reported an association between diabetes duration and various stroke subtypes among women,³ in which the risk of ischemic stroke increased from 1.5 (0–4 years) to 4.1 (>20 years). The maximum increase in the risk was seen at the 10-year mark, similar to our findings. Our cohort has men and women 40 years of age or older and representation by Hispanic, white, and black participants, as compared to the Nurses' Health study cohort, comprising predominantly white women ages 30 to 55 years at the time of enrollment.

Several potential mechanisms could explain the association of diabetes duration and stroke in our study. There is evidence of association between diabetes duration and atherosclerotic lesions, including intimal medial thickness and thin cap fibroatheromas.^{13,16} Carotid plaque thickness has been shown to predict ischemic stroke in our cohort.²⁸ In addition, hypertension is twice as prevalent among those with diabetes as in people without diabetes,²⁹ and long-term hypertension causes accelerated microvascular and macrovascular complications among those with diabetes.²⁹ The risk of microalbuminuria has been shown to increase with increasing duration of diabetes^{30,31} and microalbuminuria has been reported as a strong and independent risk factor of stroke among patients with diabetes.³² Other potential mediators may be endothelial dysfunction³³ and abnormalities in fibrinogen and clotting mechanisms.^{34,35}

Our study has public health implications. Although stroke rates have been declining among those with diabetes,³⁶ the rapid increase in diabetes incidence over the same period is leading to a higher overall stroke burden.³⁶ In recent decades, the age of onset of type 2 diabetes has decreased, paralleling the obesity epidemic in young adults.³⁷ As the population ages and the elderly live longer, more and more people will live with longer duration of the disease. It is thus important to better-understand the dynamics between diabetes, time, and

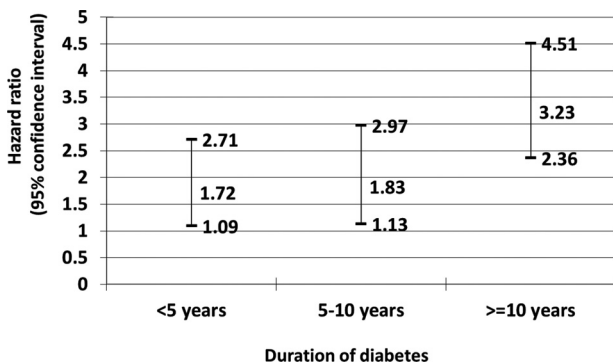


Figure. Risk of ischemic stroke and duration of diabetes.

stroke, and to emphasize the importance of interventions to prevent early diabetes. Minimizing the number of years a patient has diabetes would help combat the increase in stroke risk with each year of the disease.

Our study has several strengths. Northern Manhattan Study is designed to focus on risk factors for stroke in whites, blacks, and Hispanics living in the same community. The study has a large sample size, long duration of follow-up, minimal loss to follow-up, and detailed information on potential confounding factors. Our study design also allowed us to use diabetes as a time-dependent covariate to model risk of stroke and to study the relationship between diabetes duration and ischemic stroke among both men and women.

However, this study is not without limitations. First, because we were limited to using self-report to determine diabetes during follow-up, we may have misclassified “unaware” individuals with diabetes as not having diabetes, leading to a bias toward the null. Use of quantifiable measures of glycemic status such as fasting blood glucose or hemoglobin A1c as time-dependent covariates may have added additional prognostic information. However, our cohort may be atypical in that there was a high degree of follow-up with primary physicians (93%–96% annually), which may have led to a higher likelihood of diagnosis with diabetes. However, although we do have data collected during the annual follow-up interview on visits to primary care doctors, we do not have data on whether diabetes screening occurred during those visits. Second, the duration of follow-up may not have been long enough to bring out the difference between baseline and time-dependent models. Third, duration of diabetes at baseline was calculated based on participants’ self-reported age of onset, which is vulnerable to inaccuracy, because there is a lag time between onset and diagnosis.²⁷ The apparent threshold of 10 years identified in this study, therefore, may be an underestimate. The analysis of duration and stroke are complicated by the fact that longer duration is associated with older age, and residual confounding cannot be ruled out. We did not have sufficient numbers to detect interaction by sex, age, and race/ethnicity, and thus cannot comment on the differential effect of diabetes or its duration in segments of the cohort. However, our findings are in agreement with other large population-based cohorts.

In conclusion, use of diabetes as a time-dependent covariate adds little incremental value to using diabetes at baseline as a risk factor for stroke. Duration of diabetes, however, increases the risk of ischemic stroke, independent of coexisting risk factors. As more people have development of diabetes earlier and live longer, this relationship assumes public health importance and warrants steps to institute long-standing and sustainable lifestyle changes for primary prevention and appropriate long-term management after diagnosis.

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Disclosures

None.

References

- American Diabetes Association. Diabetes Basics: Diabetes statistics. American Diabetes Association website. Available at: www.diabetes.org/diabetes-statistics.jsp. Accessed October 4, 2009.
- Narayan KM, Boyle JP, Thompson TJ, Sorensen SW, Williamson DF. Lifetime risk for diabetes mellitus in the United States. *JAMA*. 2003;290:1884–1890.
- Janghorbani M, Hu FB, Willett WC, Li TY, Manson JE, Logroscino G, et al. Prospective study of type 1 and type 2 diabetes and risk of stroke subtypes: the Nurses’ Health Study. *Diabetes Care*. 2007;30:1730–1735.
- Jorgensen H, Nakayama H, Raaschou HO, Olsen TS. Stroke in patients with diabetes: The Copenhagen Stroke Study. *Stroke*. 1994;25:1977–1984.
- Rodriguez BL, D’Agostino R, Abbott RD, Kagan A, Burchfiel CM, Yano K, et al. 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*. 2002;33:230–236.
- Kissela BM, Khoury J, Kleindorfer D, Woo DY, Schneider A, Alwell K, et al. Epidemiology of ischemic stroke in patients with diabetes: the greater Cincinnati/Northern Kentucky Stroke Study. *Diabetes Care*. 2005;28:355–359.
- Folsom AR, Rasmussen ML, Chambless LE, Howard G, Cooper LS, Schmidt MI, et al. Prospective associations of fasting insulin, body fat distribution, and diabetes with risk of ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study investigators. *Diabetes Care*. 1999;22:1077–1083.
- Lehto S, Ronnema T, Pyorala K, Laakso M. Predictors of stroke in middle-aged patients with non-insulin-dependent diabetes. *Stroke*. 1996;27:63–68.
- 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*. 2004;164:1422–1426.
- 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) 29. *Arch Intern Med*. 1999;159:1097–1103.
- Yeh HC, Duncan BB, Schmidt MI, Wang NY, Brancati FL. Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study. *Ann Intern Med*. 2010;152:10–17.
- Fox CS, Sullivan L, D’Agostino RB Sr, Wilson PW, Framingham Heart Study. The significant effect of diabetes duration on coronary heart disease mortality: the Framingham Heart Study. *Diabetes Care*. 2004;27:704–708.
- Wagenknecht LE, D’Agostino R Jr, Savage PJ, O’Leary DH, Saad MF, Haffner SF. Duration of Diabetes and Carotid Wall Thickness The Insulin Resistance Atherosclerosis Study (IRAS). *Stroke*. 1997;28:999–1005.
- Brun E, Nelson RG, Bennett PH, Imperatore G, Zoppini G, Verlato G, et al. Diabetes duration and cause-specific mortality in the Verona Diabetes Study. *Diabetes Care*. 2000;23:1119–1123.
- Natarajan S, Liao Y, Sinha D, Cao G, McGee DL, Lipsitz SR. Sex differences in the effect of diabetes duration on coronary heart disease mortality. *Arch Intern Med*. 2005;165:430–435.
- Lindsey JB, House JA, Kennedy KF, Marso SP. Diabetes duration is associated with increased thin-cap fibroatheroma detected by intravascular ultrasound with virtual histology. *Circ Cardiovasc Interv*. 2009;2:543–548.
- Spijkerman AM, Dekker JM, Nijpels G, Jager A, Kostense PJ, van Hinsbergh VW, et al. Impact of diabetes duration and cardiovascular risk factors on mortality in type 2 diabetes: the Hoorn Study. *Eur J Clin Invest*. 2002;32:924–930.
- Emanuele NV. Duration of diabetes, glucose control and cardiovascular risk. *Diabetologia*. 2010;53:214–215.
- Sacco RL, Elkind MS, Boden-Albala B, Lin IF, Kargman DE, Hauser WA, et al. The protective effect of moderate alcohol consumption on ischemic stroke. *JAMA*. 1999;281:53–60.
- Sacco RL, Gan R, Boden-Albala B, Lin IF, Kargman DE, Hauser WA, et al. Leisure-time physical activity and ischemic stroke risk: the Northern Manhattan Stroke Study. *Stroke*. 1998;29:380–387.
- Eguchi K, Boden-Albala B, Jin Z, Di Tullio M R, Rundek T, Rodriguez C, et al. Usefulness of fasting blood glucose to predict vascular outcomes

- among individuals without diabetes mellitus (from the Northern Manhattan Study). *Am J Cardiol.* 2007;100:1404–1409.
22. Elkind MS, Sciacca RR, Boden-Albala B, Rundek T, Paik MC, Sacco RL. Moderate alcohol consumption reduces risk of ischemic stroke: The Northern Manhattan Study. *Stroke.* 2006;37:13–19.
 23. Gentry EM, Kalsbeek WD, Hogelin GC, Jones JT, Gaines KL, Forman MR, et al. The behavioral risk factor surveys: II. Design, methods, and estimates from combined state data. *Am J Prev Med.* 1985;1:9–14.
 24. Tuomilehto J, Rastenyte D, Jousilahti P, Sarti C, Vartiainen E. Diabetes mellitus as a risk factor for death from stroke. Prospective study of the middle-aged Finnish population. *Stroke.* 1996;27:210–215.
 25. Boden-Albala B, Cammack S, Chong J, Wang C, Wright C, Rundek T, et al. Diabetes, fasting glucose levels, and risk of ischemic stroke and vascular events: findings from the Northern Manhattan Study (NOMAS). *Diabetes Care.* 2008;6:1132–1137.
 26. Thorpe LE, Upadhyay UD, Chamany S, Garg R, Mandel-Ricci J, Kellerman S, et al. Prevalence and control of diabetes and impaired fasting glucose in New York City. *Diabetes Care.* 2009;32:57–62.
 27. Harris MI, Klein R, Welborn TA, Knudman MW. Onset of NIDDM occurs at least 4–7 yr before clinical diagnosis. *Diabetes Care.* 1992;15:815–819.
 28. Rundek T, Arif H, Boden-Albala B, Elkind MS, Paik MC, Sacco RL. Carotid plaque, a subclinical precursor of vascular events: the Northern Manhattan. *Stroke.* 2008;39:1200–1207.
 29. Epstein M, Sowers JR. Diabetes mellitus and hypertension. *Hypertension.* 1992;19:403–418.
 30. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Drash AL, Ellis D, et al. Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes.* 1990;39:1116–1124.
 31. Tuomilehto J, Borch-Johnsen K, Molarius A, Forsén T, Rastenyte D, Sarti C, et al. Incidence of cardiovascular disease in Type 1 (insulin-dependent) diabetic subjects with and without diabetic nephropathy in Finland. *Diabetologia.* 1998;41:784–790.
 32. Guerrero-Romero F, Rodríguez-Morán M. Proteinuria is an independent risk factor for ischemic stroke in non-insulin-dependent diabetes mellitus. *Stroke.* 1999;30:1787–1791.
 33. Clarkson P, Celermajer DS, Donald AE, Sampson M, Sorensen KE, Adams M, et al. Impaired vascular reactivity in insulin-dependent diabetes mellitus is related to disease duration and low density lipoprotein cholesterol levels. *J Am Coll Cardiol.* 1996;28:573–579.
 34. Meigs JB, Mittleman MA, Nathan DM, Tofler GH, Singer DE, Murphy-Sheehy PM, et al. Hyperinsulinemia, hyperglycemia, and impaired hemostasis: the Framingham Offspring Study. *JAMA.* 2000;283:221–228.
 35. Kannel WB, D'Agostino RB, Wilson PW, Belanger AJ, Gagnon DR. Diabetes, fibrinogen, and risk of cardiovascular disease: the Framingham experience. *Am Heart J.* 1990;120:672–676.
 36. Booth GL, Kapral MK, Fung K, Tu JV. Recent trends in cardiovascular complications among men and women with and without diabetes. *Diabetes Care.* 2006;29:32–37.
 37. Alberti G, Zimmet P, Shaw J, Bloomgarden Z, Kaufman F, Silink M, et al. Type 2 diabetes in the young: The evolving epidemic. The international diabetes federation consensus workshop. *Diabetes Care.* 2004;27:1798–1811.