

# Epidemiology of Ischemic Stroke in Patients With Diabetes

## The Greater Cincinnati/Northern Kentucky Stroke Study

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**OBJECTIVE** — Diabetes is a well known risk factor for stroke, but the impact of diabetes on stroke incidence rates is not known. This study uses a population-based study to describe the epidemiology of ischemic stroke in diabetic patients.

**RESEARCH DESIGN AND METHODS** — Hospitalized cases were ascertained by ICD-9 discharge codes, prospective screening of emergency department admission logs, and review of coroner's cases. A sampling scheme was used to ascertain cases in the out-of-hospital setting. All potential cases underwent detailed chart abstraction by study nurses followed by physician review. Diabetes-specific incidence rates, case fatality rates, and population-attributable risks were estimated.

**RESULTS** — Ischemic stroke patients with diabetes are younger, more likely to be African American, and more likely to have hypertension, myocardial infarction, and high cholesterol than nondiabetic patients. Age-specific incidence rates and rate ratios show that diabetes increases ischemic stroke incidence at all ages, but this risk is most prominent before age 55 in African Americans and before age 65 in whites. One-year case fatality rates after ischemic stroke are not different between those patients with and without diabetes.

**CONCLUSIONS** — Given the "epidemic" of diabetes, with substantially increasing diabetes prevalence each year across all age- and race/ethnicity groups, the significance of diabetes as a risk factor for stroke is becoming more evident. Diabetes is clearly one of the most important risk factors for ischemic stroke, especially in those patients less than 65 years of age. We estimate that 37–42% of all ischemic strokes in both African Americans and whites are attributable to the effects of diabetes alone or in combination with hypertension.

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While diabetes is a well known risk factor for stroke, the magnitude of risk varies widely between studies (1–9), and the impact of diabetes on stroke incidence rates is not known. The increasing prevalence of diabetes makes it one of the most serious health problems in the U.S., and its role in mac-

rovascular complications such as stroke is of increasing importance (10–12).

The prevalence of diabetes increases with age in all race/ethnicity groups (13). Within each age-group, prevalence is higher in African-American and Hispanic populations as compared with whites (13). Exploration of the race/ethnicity-specific differences in stroke risk conferred by diabetes is necessary for optimal prevention and management of stroke in these groups.

The Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) population is similar to the U.S. with regard to median age, percent African American, median household income, and percent of population below the poverty level (14,15). Thus, our study provides estimates of stroke incidence and case fatality among African Americans and whites that can be generalized to the U.S. population for these racial groups (14,15). This study will describe the epidemiology of ischemic stroke in patients with diabetes, specifically with regard to age- and race-specific stroke incidence rates.

### RESEARCH DESIGN AND METHODS

The GCNKSS population is defined as all residents of the Greater Cincinnati/Northern Kentucky region, which includes two southern Ohio counties and three contiguous northern Kentucky counties that border the Ohio River. Included in this area are 19 hospitals. Although residents of nearby counties seek care at the 19 hospitals, only residents of the five study area counties, as determined by zip code, are included as cases. This study was approved by the Institutional Review Board at all participating hospitals.

The methods of case ascertainment, case definition, and data collection have been previously reported (14,15). Briefly, study nurses retrospectively reviewed the medical records of all inpatients with primary or secondary stroke-related ICD-9 discharge diagnoses (430–438) from the 19 acute care hospitals in the study re-

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**Abbreviations:** GCNKSS, Greater Cincinnati/Northern Kentucky Stroke Study; MI, myocardial infarction; PAR, population-attributable risk; TIA, transient ischemic attack.

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

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gion. The study nurses also reviewed all autopsy cases where stroke was listed as the primary or secondary cause of death. Classification of race was as self-reported in the medical administrative record. Phase 1 of the GCNKSS involved ascertainment of hospitalized and autopsied strokes in African Americans between 1 January 1993 and 30 June 1993, and phase 2 involved collection of all strokes in the study population between 1 July 1993 and 30 June 1994. In addition to ascertaining inpatient strokes using the methodology described above, strokes in phase 2 were also ascertained in the out-of-hospital setting by monitoring all visits to 18 of the hospitals' emergency departments (excluding Cincinnati Children's Hospital), five county coroners' offices, 16 public health clinics, and 14 hospital-based outpatient clinics and family practice centers. In addition, a random sample of 50 of 878 primary care physicians' offices and 25 of 193 nursing homes in the greater Cincinnati metropolitan area were monitored. Events found only by out-of-hospital monitoring were checked against inpatient records to prevent double counting. Data from both phases 1 and 2 are presented in this report.

To qualify as an incidence case, a patient must have met the criteria for one of the five stroke categories adapted from the Classification for Cerebrovascular Diseases III and epidemiological studies of stroke: cerebral ischemia, intracerebral hemorrhage, subarachnoid hemorrhage, stroke of uncertain cause, or transient ischemic attack (TIA) (14–17).

Once potential cases were identified, the study nurse reviewed and abstracted the medical record. Data collected include stroke symptoms, past medical and surgical history, social history/habits, and disposition/outcome. Classification of a patient as having diabetes required documentation in the medical record that diabetes had been diagnosed before stroke. Diabetes was thus likely to be undercounted, because undiagnosed patients with diabetes would be classified as nondiabetic patients for this study. All borderline stroke cases were abstracted for physician review.

Ultimately, a study physician reviewed each abstract and all available neuroimaging data and then decided if a stroke or TIA had occurred. Study physicians also characterized imaging findings and assigned stroke subtype and mecha-

nism to each patient based on all available information using definitions previously reported (14,15).

In 1995, a random digit dialing telephone survey was carried out in a 2,000-person cohort of randomly selected individuals whose demographics (age, race, and sex) closely matched the expected demographics of the population of ischemic stroke patients from the study population (18). The interviewees were asked if they had been diagnosed with medical conditions known to be risk factors for stroke, such as diabetes, using interview questions adapted from the NHANES III survey (18). Using this information, age-, race-, and sex-specific prevalence rates of diabetes could be calculated. It should be noted that prevalence rates obtained from this "referent" population are taken from an older group of respondents similar to our stroke population and thus do not represent a total population prevalence rate.

#### Statistical analyses

Data were managed and analyzed using SAS version 8.1 (SAS Institute, Cary, NC). Interval variables are reported as means  $\pm$  SD. Categorical variables are reported as frequency and percent. Bivariate analyses were performed using Student's *t* test,  $\chi^2$ , or Fisher's exact test as appropriate.

We calculated incidence rates of ischemic stroke for diabetic and nondiabetic patients. The numerator was the number of ischemic strokes as determined by study physicians, tabulated for diabetic and nondiabetic patients, respectively, and further subdivided by race, age, and sex. The denominator for each rate was calculated using self-reported age-, sex-, and race-specific data obtained from the 1995 telephone survey (18) as a diabetes prevalence weighting factor for the age-, sex-, and race-specific population in 1993–1994. Age- and race-specific incidence rates and associated SEMs were calculated (sex-adjusted to the 2000 U.S. population). Disease-specific rate ratios for stroke in patients with diabetes were obtained by division of the diabetes-specific incidence rates by rates in nondiabetic patients.

A multivariable logistic regression was performed to determine the odds ratios (ORs) for ischemic stroke attributable to diabetes after controlling for age, sex, prior stroke, current smoking, hypertension, and heart disease. For this analysis,

case subjects of ischemic stroke were compared with control subjects of similar age, race, and sex from the random digit dialing survey. The model variables included previous diagnoses of diabetes, hypertension, prior stroke, or myocardial infarction (MI) and reported current smoking. Population-attributable risks (PARs) and associated 95% CIs were calculated using the prevalence data from the random digit dialing survey.

**RESULTS**— After physician review, 4,264 events met case criteria for stroke, including ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, or TIA. The Greater Cincinnati/northern Kentucky region is essentially a biracial population, and less than 1% of all stroke cases during this study period occurred in other race/ethnicity groups. The data presented hereafter include only the 2,719 African-American and white cases with ischemic stroke, 9.5% of which were ascertained only in the out-of-hospital setting (14).

Demographic characteristics of the 2,719 diabetic and nondiabetic ischemic stroke patients are presented in Table 1. African Americans were more likely to have diabetes (36% of African-American stroke patients had diabetes compared with 30% in whites;  $P = 0.005$ ). The ischemic stroke patients with diabetes were younger than the ischemic stroke patients without diabetes. They were also less likely to be current smokers at the time of their stroke and more likely to have been previously diagnosed with hypertension, high cholesterol, and MI. Among African Americans, diabetic stroke patients did not have higher rates of high cholesterol, MI, or atrial fibrillation compared with their nondiabetic counterparts, but they did have higher rates of hypertension. Among white stroke patients, those with diabetes had higher rates of hypertension, high cholesterol, and MI compared with those without diabetes.

Age-, sex- and race-specific prevalence rates of diabetes were estimated from our telephone survey information (Fig. 1). This population was similar to our stroke population with regard to age, race, and sex. Prevalence of diabetes was higher in African Americans versus whites and higher in men versus women. Prevalence generally increased with age as expected, although it should be noted that some age-, sex- and race-specific sub-

Table 1—Characteristics of ischemic stroke patients by diabetes and race

	All			Black			White		
	Diabetic	Nondiabetic	P	Diabetic	Nondiabetic	P	Diabetic	Nondiabetic	P
n	856	1,863		259	464		597	1,399	
Age (years)	70 ± 11	72 ± 15	<0.0001	67 ± 11	68 ± 17	0.6	72 ± 11	74 ± 13	<0.0001
History of hypertension	676 (79)	1,061 (57)	<0.0001	219 (84)	289 (62)	<0.0001	457 (76)	772 (55)	<0.0001
History of high cholesterol	135 (16)	177 (10)	<0.0001	35 (14)	51 (11)	0.3	100 (17)	126 (9)	<0.0001
History of myocardial infarction	193 (22)	272 (15)	<0.0001	43 (17)	75 (16)	0.9	150 (25)	197 (14)	<0.0001
History of atrial fibrillation	134 (16)	266 (14)	0.4	19 (7)	45 (10)	0.3	115 (19)	221 (16)	0.1
Current smoking	157 (18)	408 (22)	0.03	63 (24)	140 (30)	0.1	94 (16)	268 (19)	0.1

Data are means ± SD or n (%).

groups had small sample size due to this referent group being based upon the at-risk stroke population.

Age-, race-, and disease-specific incidence rates for ischemic stroke, sex-adjusted to the 2000 Census population, are displayed in Table 2. White patients with diabetes had higher stroke incidence rates compared with nondiabetic whites in every age category; a similar diabetes effect was seen in African-American patients, although the incidence rates were generally higher for each age-group than in whites. Male stroke risk was substantially higher than female stroke risk, and this difference was accentuated in African Americans compared with whites (data not shown).

Race-specific risk ratios (RRs) are displayed in Table 2. Risk for ischemic stroke in white diabetic patients is higher at every age-group compared with nondiabetic patients, with a maximum RR of 5.3 in the 45- to 54-year age-group. Among African Americans, risk in diabetic compared with nondiabetic patients is greater

in all age-groups except the youngest and oldest, with a maximum RR of 9.9 in the 35- to 44-year age-group. A substantial peak in stroke risk is seen in the 35- to 54-year age-groups in African Americans and in the 45- to 64-year age group in whites.

Case fatality rates were determined. Diabetic patients do not have significantly different case fatality rates in the first year after ischemic stroke when compared with nondiabetic patients overall or when subdivided by race. Given the substantial risk for stroke conferred by diabetes, this suggests that there are proportionately more patients with diabetes surviving with disability after stroke compared with nondiabetic patients.

Multivariable PARs are presented in Table 3. It can be seen that the OR for stroke due to a history of both diabetes and hypertension is substantially greater than for either condition alone. Diabetes alone has a higher OR than hypertension alone, but PAR is higher for hypertension given the prevalence of hypertension in

both races. Diabetes and hypertension, either alone or in combination, account for 37–42% of the PARs in both race/ethnicity groups.

**CONCLUSIONS**— Diabetic patients with ischemic stroke are younger, more likely to be African American, and more likely to have hypertension, MI, and high cholesterol than their nondiabetic counterparts. Our data are in keeping with other studies in showing a significantly increased risk for ischemic stroke conferred by diabetes but are the first to estimate diabetes-specific incidence rates in a race- and age-specific fashion. Our data demonstrate a race-specific effect, with higher risk for African Americans with diabetes, and an age-specific risk, with substantially increased risk for diabetic patients less than age 65 compared with those without diabetes. Finally, the case fatality after ischemic stroke was not found to be higher in patients with diabetes. Given that in many studies surviving stroke patients with diabetes have been shown to have worse functional outcome, diabetic patients are more likely to survive with disability after ischemic stroke.

Prevalence data from our population survey (subjects with similar demographics to stroke patients) show that diabetes is most common in African-American men, prevalence is similar in white men and African-American women, and white women are least likely to have diabetes. These results are similar to findings in the general population (13) and are helpful in understanding the imbalance in stroke risk factors observed. Diabetes is part of the “metabolic syndrome,” which also includes high blood pressure, high cholesterol, and obesity. African Americans are more likely to have this syndrome than whites (19), and patients with diabetes

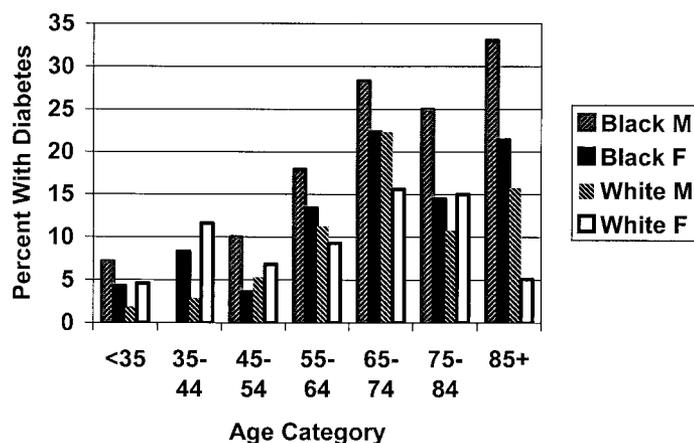


Figure 1—Age-, race-, and sex-specific prevalence of diabetes in 1995 telephone survey (subjects similar with regard to age, race, and sex to the 1993–1994 stroke population).

**Table 2—Incidence rates of ischemic stroke in nondiabetic and diabetic subjects per 100,000 (95% CI) and RRs for ischemic stroke with diabetes**

Age-group	Black nondiabetic	Black diabetic	Black risk ratio for diabetes	White nondiabetic	White diabetic	White risk ratio for diabetes
<35 years	9 (3–14)	0	0 (–1.0 to 1.0)	3 (1–4)	6 (–6 to 17)	2.1 (0.8–3.4)
35–44 years	42 (18–66)	413 (38–788)	9.9 (8.5–11.3)	11 (6–16)	28 (0–56)	2.6 (1.1–4.1)
45–54 years	130 (75–185)	1,079 (500–1,659)	8.3 (7.3–9.3)	56 (42–69)	295 (172–418)	5.3 (3.9–6.7)
55–64 years	322 (220–425)	930 (515–1,344)	2.9 (1.8–4.0)	152 (125–178)	708 (539–878)	4.7 (3.4–6.0)
65–74 years	616 (451–781)	1,731 (1,238–2,224)	2.8 (1.8–3.8)	404 (355–453)	896 (741–1,051)	2.2 (1.1–3.3)
75–84 years	1,047 (761–1,333)	1,858 (1,044–2,673)	1.8 (0.8–2.7)	828 (741–915)	1,939 (1,621–2,257)	2.3 (1.5–3.2)
≥85 years	2,033 (1,280–2,786)	1,686 (466–2,907)	0.8 (0.0–1.6)	1,438 (1,248–1,628)	3,308 (2,330–4,285)	2.3 (1.7–2.9)

are likely to have the other risk factor components of this syndrome. With regard to other risk factor imbalances among our ischemic stroke patients, whites had more MIs and atrial fibrillation. While this may be a race-specific effect that has been reported previously, it may also be due in part to the younger age of African-American stroke patients as compared with whites.

Since diabetes is more prevalent in African Americans and other race/ethnicity groups compared with whites, our study can be used to measure the attributable risk of diabetes on stroke incidence in African Americans and whites. A multivariate PAR analysis with regard to ischemic stroke among predominantly white patients in Rochester, Minnesota, found a 5% PAR due to diabetes (3). In the Northern Manhattan Stroke Study, a similar multivariable analysis found PARs of 14 and 10% conferred by diabetes for Caribbean-derived African Americans and Hispanics, respectively, but no appreciable PAR for whites (20). Our study finds multivariable PARs of 20–21% for African-American and white patients who have the combination of diabetes and hy-

pertension. Diabetes and hypertension seen alone account for an additional 15–22% PAR that varies by race. The disparity seen between our results and the previously published analyses may be related to how our analysis was performed and in particular due to the referent population that was used. However, the difference seen might also be related to the varied demographics of the populations being studied, including variations in diabetes prevalence and stroke incidence. Our white population has lower educational achievement and lower measures of socioeconomic status compared with Rochester, Minnesota (16), and has higher incidence of stroke compared with the white population in Northern Manhattan (21). The African-American population of Northern Manhattan is predominately of Caribbean descent, and our population is predominately African American (21).

Combining age- and race-specific prevalence of diabetes (22) with the projected U.S. population for 2002 and our ischemic stroke incidence rates displayed in Table 2, we conservatively estimate that a minimum of 143,000–154,000 isch-

emic strokes occurred in diabetic patients in 2002 in the U.S. This represents 20–22% of the 705,000 strokes estimated to occur in 2002 (14). However, we only classified those patients who had previously been diagnosed with diabetes as “diabetic stroke patients.” Certainly there are many patients who had not been diagnosed with diabetes at the time of their ischemic stroke, and thus our incidence rates, RRs, and estimate of diabetic strokes in 2002 are underestimates.

Given the “epidemic” of diabetes, with substantially increasing diabetes prevalence each year across all age- and race/ethnicity groups, the importance of diabetes as a risk factor for stroke is increasing. Diabetes is clearly one of the most important risk factors for ischemic stroke, especially for those occurring before age 65. We estimate that 25–26% of all ischemic strokes are attributable to the effects of diabetes alone or in combination with hypertension, and this may well be an underestimate. Race-specific data about stroke incidence in patients with diabetes must continue to be studied to see if incidence rates are changing over time.

**Table 3—Multivariable logistic regression model for ischemic stroke\***

	African-American patients				Caucasian patients			
	OR	95% CI	PAR	95% CI	OR	95% CI	PAR	95% CI
Age (per year)	1.02	1.01–1.03			1.06	1.05–1.06		
Male	1.2	1.0–1.6			1.4	1.2–1.6		
History of prior stroke	4.7	3.3–7.0	22.3	18.8–25.7	3.6	2.8–4.7	14.8	13.4–16.1
History of both diabetes and hypertension	3.0	2.1–4.3	21.1	18.1–24.0	4.5	3.5–5.8	20.6	19.0–22.1
History of diabetes only	2.7	1.5–5.2	5.6	3.6–7.5	2.1	1.5–3.0	5.2	4.3–6.1
History of hypertension only	1.3	0.9–1.7	9.8	3.7–15.5	1.6	1.4–1.9	16.2	13.8–18.4
Current smoking	1.5	1.1–1.9	10.9	6.5–15.2	1.7	1.4–2.2	12.5	10.7–14.2
History of myocardial infarction	1.1	0.8–1.7	1.4	0–3.6	1.1	0.9–1.4	1.0	0–2.0

\*PARs calculated from GCNKSS prevalence data.

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