Clinical Sciences

Diabetes Mellitus
A Risk Factor for Ischemic Stroke in a Large Biracial Population

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Background and Purpose—We previously reported increased incidence of ischemic stroke among both blacks and whites with diabetes mellitus, especially in those aged <55 years. With rising prevalence of diabetes mellitus in the past decade, we revisit the impact of diabetes mellitus on stroke incidence in the same population (≈1.3 million) 5 and 10 years later.

Methods—This is a population-based study. First ischemic strokes among black and white residents of the 5-county Greater Cincinnati/Northern Kentucky region, aged ≥20 years, for periods 7/1993 to 6/1994, 1999, and 2005, were included in this analysis. Incidence rates were adjusted for sex, race, and age, as appropriate, to the 2000 US population.

Results—History of diabetes mellitus among first ischemic strokes was reported for 493/1709 (28%) in 1993/1994, 522/1778 (29%) in 1999, and 544/1680 (33%) in 2005. Risk ratios (95% confidence interval) for rates of stroke in those with versus without diabetes mellitus for blacks reduced significantly from 5.6 in 1993/1994 to 3.2 in 2005; for whites the risk ratio remained stable at 3.8 in 1993/1994 and 2005. However, risk ratios varied with age, with an overall 5- to 14-fold increased risk observed in those aged 20 to 65 years.

Conclusions—Those with diabetes mellitus remain at greatly increased risk for stroke at all ages, especially <65 years, regardless of race. The rates and risk ratios for 1999 and 2005, although similar to those previously reported for the mid-1990s, take on increased significance, given the epidemic of diabetes mellitus and metabolic syndrome throughout the US and the world. (Stroke. 2013;44:1500-1504.)

Key Words: black ■ diabetes mellitus ■ incidence ■ ischemic stroke ■ population based

We previously reported an increased incidence of ischemic stroke among both blacks and whites with diabetes mellitus. We found significant variation by age, with high risks for the youngest (especially those <55). More recently, we also reported on increasing incidence of stroke overall in this relatively younger population. In addition, George et al, using the Nationwide Inpatient Sample database, reported an overall increase in hospitalization rates for ischemic stroke between 1995 and 1996 and 2007 to 2008 for age groups 5 to 14, 15 to 34, and 35 to 44 years and a concomitant increase in prevalence rate of diabetes mellitus. Diabetes mellitus, perhaps the second most important risk factor for stroke, is highly associated with other comorbidities, including hypertension. The prevalence of diabetes mellitus has been increasing during the past decade in all age groups but particularly in the younger population. Taken together with our previous findings, one might expect an increasing incidence of stroke, especially in the younger age ranges, related to this higher prevalence of diabetes mellitus. In contrast, recent studies, including our own, have shown that the overall incidence of stroke has been decreasing in the white population but has remained stable in the black population. Further examination of our rates by age has revealed decreasing incidence in the older white population. Because of the rising epidemic of diabetes mellitus in the past decade, we decided to revisit the impact of diabetes mellitus on stroke incidence in the same region of 1.3 million people, 5 and 10 years after the initial observation. We sought to examine any potential trends of increasing stroke incidence in those with pre-existing diabetes. The Greater Cincinnati Northern Kentucky Stroke Study (GCNKSS) population reflects the US population with respect to percentage of blacks, median age and income, and educational level. Thus, any changes observed in our
population may be generalizable to the US black and white population.

Methods

The GCNKSS population is defined as all residents of 2 counties in southwest Ohio (1 of which includes the city of Cincinnati) and 3 contiguous counties in northern Kentucky, separated by the Ohio River. Only residents of the 5 study area counties were eligible to be counted as cases for this study. This study was approved by the institutional review board at all participating hospitals. The methodology and definitions used for our study have been previously reported.\textsuperscript{12} Study nurses retrospectively reviewed the medical records of all inpatients and hospital emergency department visits with primary or secondary stroke-related International Classification of Diseases-Ninth Revision (ICD-9) discharge diagnoses (codes 430–436) from the acute-care hospitals in the study region. This included 19 hospitals in 1993/1994, 18 in 1999, and 17 in 2005; the decreasing numbers are because of consolidations and closings. Strokes were also ascertained by monitoring stroke-related stroke visits to all public health clinics and based outpatient clinics. Cases where stroke was listed as the primary or secondary cause of death by 1 of the 5-county coroners’ offices were also included. In addition, monitoring was performed by examining the records of potential stroke cases in a random sample of primary care physicians’ offices and nursing homes in the GCNK region. Sampling was necessary given the large number of physician offices and nursing homes in the region; we have previously described this sampling in detail.\textsuperscript{12} Sites were selected randomly, for each study period, by the study statistician from a list generated from a combination of the local yellow pages and the American Medical Association listing of physicians in the region. The random sample consisted of 50 of the 878 primary care physicians’ offices and 25 of the 193 nursing homes in the study region, in 1993/1994. The numbers were 37 of the 849 primary care physicians’ offices and 23 of the 171 nursing homes in 1999; and 51 of the 832 primary care physicians’ offices and 26 of the 126 nursing homes in 2005. All events were cross-checked within and between sources to prevent double counting. Thus, the total number of first-time strokes in this area is represented; the out-of-hospital ascertained strokes account for between 10% and 20% of the strokes in our population in the 3 study periods.\textsuperscript{12}

To qualify as a case, a patient must have met the criteria for 1 of the 5 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 (symptoms lasting <24 hours).\textsuperscript{1,2,13,15} Once potential cases were identified, a study nurse reviewed and abstracted the medical record. All probable and borderline stroke cases were abstracted for physician review. Data collected included stroke symptoms, past medical and surgical history, and disposition/outcome; also medical and vascular risk factors as recorded in the medical record. Patients were identified as having diabetes mellitus on the basis of the documentation in the medical record that diabetes mellitus had been diagnosed before the stroke. It is likely that diabetes mellitus was undercounted, as only those patients with a diagnosis of diabetes mellitus documented in the medical record were classified as having diabetes mellitus (undiagnosed diabetes mellitus, ie, elevated fasting glucose or glycohemoglobin A1C, was not classified as diabetes mellitus for this study). The classification of race was as self-reported in the medical administrative record. A study physician reviewed each abstract and all available neuroimaging data to determine whether a stroke or transient ischemic attack occurred. Study physicians also characterized imaging findings and assigned stroke subtype and mechanism to each patient on the basis of all available information. To ensure consistency over time, only those ischemic strokes identified by the strict clinical definition were included in this analysis.\textsuperscript{1,2,13,15} Because we were tracking incident events, recurrent cases of ischemic stroke were excluded.

Results

Among black and white area residents aged ≥20 years identified in the study area, there were 1709 first-ever ischemic strokes in 1993/1994, 1778 in 1999, and 1680 in 2005. In 1993/1994, 493 (28%) had a documented history of diabetes mellitus diagnosed before stroke, compared with 522 (29%) in 1999 and 544 (33%) in 2005 (P for trend=0.01). This trend of increasing diabetes mellitus in stroke subjects mirrors the national trend of increasing diabetes mellitus in the US population.\textsuperscript{19} Data from NHANES III, 1999 to 2000, and 2005 to 2006 showed a similar increase in rate of diabetes mellitus from the population aged ≥20 years of 5.1%, 5.9%, and 7.7%. The demographics of the stroke patients with and without diabetes mellitus are shown in Table 1. In all 3 study periods, patients with diabetes mellitus were somewhat younger on average than those without diabetes mellitus, but this was only statistically significant in 1999. Sex distribution was similar over time, but the proportion of blacks with diabetes mellitus was higher than that of whites in all 3 study periods (18.8% versus 15.5% in 1993/1994; 19.0% versus 13.8% in 1999, and 26.7% versus 16.2% in 2005; \(P<0.001\) for 1999 and 2005).

Distributions of stroke risk factors by study period and diabetes mellitus status are also shown in Table 1. The proportions of stroke risk factors were higher in stroke patients with diabetes mellitus, compared with those without

Statistical Analyses

Data management and descriptive and comparative analyses were performed using SAS versions 8.02 and 9.2, respectively (SAS Institute, Inc, Cary, NC). Population estimates were obtained by including the sampling weights in all analyses as dictated by the study design. The sampling weights were 1 for all strokes except those identified through the physician’s office or nursing home monitoring. The sampling weight is calculated, by study period, as the number in the area divided by number sampled, as described above.

Incidence rates of ischemic stroke were estimated separately for patients with and without diabetes mellitus. The numerator was the weighted number of first ischemic strokes as determined by physician review, further classified by diabetes mellitus status. The denominator by sex, race, and age group was extracted from the US Census Bureau website (http://www.census.gov) for 1993, 1994, 1999, and 2005 for the 5-county area. The denominators for the populations with and without diabetes mellitus were calculated on the basis of age-, sex-, and race-specific rates of diabetes mellitus in the NHANES III, 1999 to 2000, and 2005 to 2006 databases as appropriate, for the study year. Diabetes mellitus was defined as response to the NHANES question “other than during pregnancy have you ever been told by a doctor or other health professional that you have … diabetes or sugar diabetes?” as this was thought to best reflect our chart abstraction information. NHANES has been used extensively to report population-based prevalence of diabetes mellitus and other chronic diseases.\textsuperscript{6,16}

Stroke incidence rates were age, sex, and race adjusted to the 2000 US population, as appropriate. SEs for incidence rates were estimated assuming a Poisson distribution. Risk ratios for stroke in patients with diabetes mellitus were obtained by division of the incidence rates for those with diabetes mellitus by the incidence rates for those without diabetes mellitus, and SEs were estimated using the 6 method.\textsuperscript{17} Generalized estimating equations\textsuperscript{18} were used to examine the bivariate differences between stroke patients with and without diabetes mellitus and the trends over time. This allowed inclusion of a clustering variable to account for the sampling scheme defined above. The working correlation structure giving the best model fit was obtained. Data are reported as raw numbers with weighted percentages or weighted means and the associated SE.
diabetes mellitus, except for atrial fibrillation and current smoking. The diagnoses of hypertension and high cholesterol increased over time for both those with and without diabetes mellitus, and remained significantly increased in each period for patients with diabetes mellitus, compared with those without diabetes mellitus. There was an overall decrease in history of myocardial infarction over time, it remained increased in those with diabetes mellitus compared with those without. Rates of atrial fibrillation did not change over time and were not different by diabetes mellitus status. Current smoking rates increased over time for both those with and without diabetes mellitus, and were consistently higher in those without diabetes mellitus, although only statistically significant in 2005.

Age and sex-adjusted incidence rates of first-ever ischemic stroke for populations both with and without diabetes mellitus are shown in Table 2. Incidence rates are shown for the study years 1993/1994, 1999, and 2005. Diabetes mellitus confers a consistent, significantly higher incidence of stroke in all study periods.

In the population with diabetes mellitus, overall incidence rates for stroke for blacks decreased significantly during the study periods, from 1331/100,000 (95% confidence interval, 1037, 1624) in 1993/94 to 617/100,000 (496, 737) in 2005, whereas the incidence rates for the white population remained unchanged, 549/100,000 (484, 614) in 1993/1994 and 504/100,000 (443, 565) in 2005. This is in contrast to the overall incidence rates in the population without diabetes mellitus, where the black rate did not change significantly; 241/100,000 (208, 275) in 1993/1994 and 216/100,000 (185, 246) in 2005. However, the rate in the white population decreased significantly from 169/100,000 (159, 246) in 1993/1994 to 145/100,000 (136, 154) in 2005.

Stroke incidence rates by age group (Table 2), for both the black and white populations with diabetes mellitus, remain unchanged over time for those aged <65 years but decrease significantly in the older age group. Stroke incidence rates for those without diabetes mellitus for the black population show no significant change during the 15-year period, but there is a significant increase in incidence of stroke seen in the white population.
population aged <65 years, in contrasted to a significant decrease in incidence in those ≥65 years.

The risk ratios for incidence rate of stroke for those with diabetes mellitus compared with those without diabetes mellitus are presented in Table 3. The excess risk for those with diabetes mellitus is decreasing in the black population but remains stable in the white population over time. The overall risk ratio for blacks decreased significantly from 5.6 in 1993/1994 to 3.2 in 2005; in whites the risk ratio was 3.8 in both 1993/1994 and 2005. Age-specific risk ratios by race also show a significant decrease over time in the black population aged ≥65 years but not for those <65 years. In the white population those aged <65 years have a 12- to 14-fold increase in stroke incidence during the study periods when diagnosed with diabetes mellitus before stroke; the excess risk is under 3 in the older age group but does not change significantly over time in either age group.

Data were collapsed over the years to examine the effect of age more closely. The risk ratios reiterate the increased risk for stroke conferred by diabetes mellitus in the white population compared with blacks in the age groups <65 years, these are statistically significant in the groups 45 to 54 years and 55 to 64 years. In the oldest age group ≥75 years, a significantly increased risk ratio for the white population compared with the black population is again observed. The overall risk ratio conferred by diabetes mellitus for whites is significantly greater than that for blacks. Data are presented in Table I in the online-only Data Supplement.

### Discussion

As we had shown before,¹ the population with diabetes mellitus is at substantially increased risk for stroke. Our data highlight the increasing prevalence of diabetes mellitus among stroke patients over time in line with the epidemic of diabetes mellitus seen in the general population. We show higher prevalence of risk factors in patients with diabetes mellitus, and increasing hypertension and high cholesterol in all stroke patients over time. Furthermore, our data demonstrate a continued 3- to 4-fold increased incidence rate of ischemic stroke for patients with diabetes mellitus as compared with those without diabetes mellitus. The excess risk is seen across all ages, but it is particularly striking in the age group <65 years. We are also seeing a shift over time with evidence of higher ischemic stroke risk in whites compared with blacks conferred by diabetes mellitus at virtually all ages.

Our data are of great public health importance given the well-publicized epidemic of diabetes mellitus and obesity, or alternatively of the metabolic syndrome.¹⁹,²⁰ Diabetes mellitus is clearly an important risk factor for stroke especially in those aged <65 years.²,³ This finding is consistent with those reported from studies in the United Kingdom and Europe.²¹,²² In addition, it has been shown that diabetes mellitus is an important risk factor associated with poor poststroke outcomes and disability.²³–²⁶ Thus, higher rates of stroke in patients with diabetes mellitus, especially in younger patients, may be associated with a higher burden of disability, productive life-years lost, and higher cost to society. Given the increasing prevalence of diabetes productive life-years lost in 2005 compared with 1993/1994, we estimate that there were an additional 25,000 strokes in 2005 associated with this increase.

Our study has several limitations. We have the potential for increased awareness and increase in physician diagnosis of diabetes productive life-years lost and other risk factors over time, which may skew the risk ratios. In addition, we do not know duration or time since diagnosis of diabetes productive life-years lost, or can we estimate the rate of undiagnosed diabetes mellitus at initial presentation with stroke for all the periods studied. Finally, because our methodology is retrospective, there is the risk of underdocumentation bias, which would result in our diabetes mellitus–specific rates being underestimates. Nevertheless, weaknesses are balanced by strengths, including the population-based nature of our study, and the ability to assess changes over time with little change in methodology for both stroke and diabetes mellitus ascertainment.

### Conclusions

Diabetes mellitus is not only a highly important risk factor for ischemic stroke at all ages, but also especially so in those aged <65 years with risk ratios showing more than a 5-fold risk. Our data support diabetes mellitus as a very important preventable ischemic stroke risk factor. Thus, physicians caring for patients at risk for stroke should be vigilant for diabetes mellitus and other concurrent stroke risk factors that tend to cluster with diabetes mellitus. We see a significant risk difference where diabetes mellitus may confer more risk to whites than blacks for stroke, which requires further study.

### Sources of Funding

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### Disclosures

Drs Khoury, Kleindorfer, Moomaw, Flaherty, Kissela, and K. Alwell, BSN, receive research support from the National Institutes of Health. The other authors have no conflicts to report.

### Table 3. Risk Ratios (95% Confidence Interval) for Ischemic Stroke in Those With Diabetes Mellitus Versus Without Diabetes Mellitus

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<td>&lt;65 y*</td>
<td>8.4 (4.8, 11.9)</td>
<td>9.8 (6.6, 13.0)</td>
<td>5.2 (3.6, 6.8)</td>
<td>12.4 (9.4, 15.5)</td>
<td>14.2 (10.7, 17.7)</td>
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<td>≥65 y*</td>
<td>5.9 (4.1, 7.6)</td>
<td>1.2 (0.8, 1.6)</td>
<td>2.1 (1.5, 2.7)</td>
<td>2.8 (2.4, 3.2)</td>
<td>2.5 (2.2, 2.9)</td>
<td>2.7 (2.1, 3.4)</td>
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<td>All ages†</td>
<td>5.6 (4.2, 7.1)</td>
<td>2.8 (2.0, 3.5)</td>
<td>3.2 (2.4, 3.9)</td>
<td>3.8 (3.2, 4.3)</td>
<td>4.0 (3.5, 4.6)</td>
<td>3.8 (3.3, 4.3)</td>
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</table>

*Sex adjusted to the 2000 US population.
†Sex and age adjusted to the 2000 US population.
References


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TITLE: Diabetes: a Risk Factor for Ischemic Stroke in a Large Bi-Racial Population

COVER TITLE: Diabetes: a Risk Factor for Ischemic Stroke

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TABLES:
Table S1: Incidence rates by age and race (95% confidence interval (CI)) for ischemic stroke in those with diabetes vs. without diabetes; combined over study periods

TABLES: 1
Supplemental Table S1: Incidence rates by age and race (95% confidence interval (CI)) for ischemic stroke in those with diabetes vs. without diabetes; combined over study periods

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<td>20 – 44 years*</td>
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*Sex adjusted to the 2000 US population
#Sex and age adjusted to the 2000 US population
†Rates based on samples of <30 should be treated with caution