

Regional Differences in Diabetes as a Possible Contributor to the Geographic Disparity in Stroke Mortality

The REasons for Geographic And Racial Differences in Stroke Study

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Background and Purpose—Diabetes and hypertension impart approximately the same increased relative risk for stroke, although hypertension has a larger population-attributable risk because of its higher population prevalence. With a growing epidemic of obesity and associated increasing prevalence of diabetes that disproportionately impacts the southeastern Stroke Belt states, any potential contribution of diabetes to the geographic disparity in stroke mortality will only increase.

Methods—Racial and geographic differences in diabetes prevalence and diabetes awareness, treatment, and control were assessed in the REasons for Geographic And Racial Differences in Stroke study, a national population-based cohort of black and white participants older than 45 years of age. At the time of this report, 21 959 had been enrolled.

Results—The odds of diabetes were significantly increased in both white and black residents of the stroke buckle (OR, 1.26; [1.10, 1.44]; OR, 1.45 [1.26, 1.66], respectively) and Stroke Belt (OR, 1.22; [1.09, 1.36]; OR, 1.13 [1.02, 1.26]) compared to the rest of the United States. In the buckle, regional differences were not fully mediated and remained significant when controlling for socioeconomic status and risk factors. Addition of hypertension to the models did not reduce the magnitude of the associations. There were no significant differences by region with regard to awareness, treatment, or control for either race.

Conclusions—These analyses support a possible role of regional variation in the prevalence of diabetes as, in part, an explanation for the regional variation in stroke mortality but fail to support the potential for a contribution of regional differences in diabetes management. (*Stroke*. 2008;39:1675-1680.)

Key Words: diabetes ■ geography ■ racial differences

The prevalence of diabetes in the United States has increased substantially in the past several decades,^{1–7} corresponding to dramatic increases in obesity rates.⁸ Prevalence of diabetes varies by race, with higher rates in both male and female non-Hispanic blacks than non-Hispanic whites.^{9,10} Diabetes is an independent risk factor for stroke and has been shown to increase the risk of stroke with a relative risk ranging from 1.8 to >8-fold, with larger increased risk in younger age groups.^{11,12}

Stroke mortality varies by race and by geographic region in the United States, with the highest rates in the “buckle” of the Stroke Belt (coastal plain region of North Carolina, South Carolina, and Georgia) and the Stroke Belt states (remainder of North Carolina, South Carolina, and Georgia, plus Alabama, Mississippi, Tennessee, Arkansas, and Louisiana). Although the variation in stroke mortality by race and region is well-described, the underlying causes are not understood.^{13,14}

Hypertension and diabetes impart approximately the same increase in the relative risk for stroke;¹⁵ however, hypertension has a larger population-attributable risk because of its higher prevalence.^{16,17} There is evidence of an increasing prevalence of diabetes that is likely associated with the increasing obesity epidemic and, as such, the importance of diabetes as a stroke risk factor is likely to grow and the impact may be larger in states with a higher prevalence of obesity. The Behavioral Risk Factor Surveillance System reports diabetes and obesity by state on the basis of self-reported disease status and body weight.¹⁸ Based on these data the prevalence rate of diabetes (defined as having been told by a physician that you have diabetes) was calculated for adults aged 20 and older, the median prevalence rate was 6.6%, and all 8 Stroke Belt states (North Carolina, South Carolina, Georgia, Tennessee, Alabama, Mississippi, Arkansas, and Louisiana) reported rates higher than this median rate. Likewise, the median percent obese was 21.6, with all of the

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“Stroke Belt states” reporting rates substantially higher than this average. Hence, with hypertension and diabetes imparting approximately the same relative risk, and with a growing epidemic of obesity that is disproportionately impacting the southeastern Stroke Belt states, the higher-than-expected rate of diabetes in the southeastern Stroke Belt states suggest that diabetes may be a major contributor to the geographic disparity in stroke mortality.

Few studies have described geographic variations in the prevalence of diabetes in the United States, and most of those available have relied on self-reported diabetes status.^{9,19,20} We previously reported higher prevalence of diabetes in the Stroke Belt than in the rest of the United States based on measured diabetes status in a large national sample of blacks and whites.²¹ In this report we investigate these differences in greater detail and additionally assess if there are regional differences in diabetes management. Also, there are well-known geographic differences in the prevalence of hypertension, with a higher prevalence in the Stroke Belt region.^{22,23} Because hypertension and diabetes frequently cluster in the same individuals, these regional differences in hypertension could introduce regional differences in diabetes. As such, in the final modeling step we also establish if the regional differences in diabetes are independent of regional differences in hypertension, that is, whether there is a higher prevalence of diabetes in the southeastern United States that is not only a corollary of the known higher prevalence of hypertension.

Methods

Data from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study were used to estimate the prevalence and management rates for diabetes in the United States population of blacks and whites. REGARDS is a national population-based longitudinal cohort study designed to examine the causes for geographic and racial differences in stroke mortality with a recruitment goal of 30 000 individuals older than 45 years of age, with equal representation of whites and blacks and men and women.²⁴ Twenty percent of the sample is selected from the Stroke Belt, 30% from the Stroke Belt states, and the remaining 50% from the other 40 contiguous states. Individuals are recruited from commercially available lists of residents using a combination of mail and telephone contact. For those agreeing to participate, demographic information, medical history, and measures of cognitive function and quality of life are obtained by computer-assisted telephone interview. Approximately 1 month after the telephone interview, physical measures including height, weight, blood pressure, and fasting morning blood samples were collected at an in-home examination. After centrifugation, blood samples were shipped overnight on ice packs to a central laboratory for analysis. Glucose was measured in serum using colorimetric reflectance spectrophotometry on the Ortho Vitros 950 IRC Clinical Analyzer (Johnson & Johnson Clinical Diagnostics) with a coefficient of variation of 1%.

The study methods were reviewed and approved by the Institutional Review Boards at the collaborating institutions. Additional methodological details have been provided previously.²⁴ Enrollment began in February 2003 and at the time of this analysis, baseline and in-home examinations were complete for the first 21 959 participants. Of these participants, 1053 (4.8%) were excluded because of missing data regarding fasting status ($n=125$) or glucose measurements ($n=928$) for a study cohort of 20 906 participants.

Definitions

Diabetes status was ascertained using data from the baseline telephone interview and the in-home examination. On the baseline

interview, participants were asked if they had ever been told by a doctor that they had diabetes or high blood sugar. If female they were asked if this was only during pregnancy. All people who responded “yes” to the initial question regarding diabetes outside of pregnancy were then asked if they were using diabetes medication and specifically if they were using diabetes pills or insulin. Diabetes was then defined as the blood measurement fasting glucose >126 mg/dL, nonfasting glucose >200 mg/dL, or current diabetes treatment with pills or insulin.

Among persons with diabetes, awareness was defined as having responded positively to “have you ever been told by a doctor that you had diabetes or high blood sugar?” Among individuals who were “aware” of their diabetes status, treatment was then defined as self-report of taking diabetes pills or insulin. Finally, among those being treated for diabetes, control was defined as having fasting glucose levels within the bounds of ≤ 126 mg/dL or nonfasting glucose ≤ 200 mg/dL.

Blood pressure was the average of 2 measurements taken after the participant was seated for 5 minutes, measured by a trained technician using a standard protocol and regularly tested aneroid sphygmomanometer. Hypertension was defined as SBP ≥ 140 mm Hg, or DBP ≥ 90 mm Hg, or self-report of current use of hypertension medication (a positive response to “has a doctor or other health professional ever told you that you have high blood pressure?”, and to “Are you currently taking medication for high blood pressure?”).

Variables that could potentially confound the relationship between region and diabetes were categorized into 3 groups: demographic factors, including age (categorized as 45 to 54, 55 to 64, 65 to 74, and 85 and older), gender and race (white or black); socioeconomic factors (SES), including years of education (less than high school, high school graduate, some college or college graduate), income status ($< \$25$ 000, $\$25$ 000 to $\$50$ 000, $> \$50$ 000), and whether the participant had health insurance (answered “yes” to “Do you have any kind of healthcare coverage such as health insurance, an HMO, or a government plan like Medicare or Medicaid?”), and risk factors of interest, including cigarette smoking (categorized as never, past, or current), alcohol use (never, current or past), body mass index (categorized as normal ≤ 24.9 kg/m², overweight 25 to 29.9 kg/m², or obese ≥ 30 kg/m²), and frequency of exercise (categorized by the question “How many times per week do you engage in intense physical activity, enough to work up a sweat?” into never, < 5 times per week, and ≥ 5 times per week).

Statistical Analysis

The cohort was described using frequencies and percents for categorical variables. Univariate logistic regression was used to assess the relationship between diabetes and region of residence. Multivariable logistic regression was then performed to estimate the relation between region and diabetes, after adjustment for groups of potential confounders. These analyses were performed using a series of models that progressed from considering region alone to adding demographic factors, then adding socioeconomic factors, and then adding the risk factors of interest. Finally, hypertension was added to the model to determine if any observed regional differences were independent of hypertension status. Differences in diabetes awareness and treatment and glucose control by region were also assessed using an incremental series of models that first looked at region alone, then added in demographic factors, and finally added in SES factors. Because race varies by region, all analyses were stratified by race.

Results

Of the 20 906 eligible participants, 4500 (21.5%) had diabetes. The distribution of demographic and risk factor characteristics and the prevalence of diabetes within each characteristic are given in Table 1. Statistically significant ($P<0.0001$) univariate differences in diabetes rates existed for all the characteristics in Table 1 with the exception of region and insurance status. The factors that had the largest

Table 1. General Characteristics of the REGARDS Cohort by Diabetes Status

	Total REGARDS Participants	With Diabetes	
		N	%
All	16 406	4500	21.5
Region			
Stroke Buckle*	2772	822	22.9
Stroke Belt†	5797	1595	21.6
Non-Belt	7821	2080	21.0
Race			
White	10 384	1946	15.8
Black	6017	2552	29.8
Age group			
45–54	1498	260	14.8
55–64	6549	1730	20.9
65–74	5357	1715	24.3
75–84	2651	731	21.6
85+	346	61	15.0
Gender			
Male	7775	2293	22.8
Female	8628	2206	20.4
Income			
<25 000	4324	1713	28.4
25 000–50 000	5129	1349	20.8
>50 000	5019	897	15.2
Education			
No high school degree	1871	931	33.2
Graduated high school	4178	1258	23.1
Some college	4387	1199	21.5
Graduated college	5961	1104	15.6
Health insurance			
Yes	15 422	4226	21.5
No	973	271	21.8
Category of BMI			
Normal	4717	525	10
Overweight	6367	1388	17.9
Obese	5153	2521	32.9
Days per week of intense physical activity			
Never	5258	1823	25.7
1–4 d/wk	7047	1718	19.6
>5 d/wk	3799	877	18.8
Alcohol use			
Never	4466	1634	26.8
Current	9146	1678	15.5
Past	2794	1188	29.8
Smoking status			
Current	2396	627	20.7
Past	6720	2049	23.4
Never	7226	1811	20

(Continued)

Table 1. Continued

	Total REGARDS Participants	With Diabetes	
		N	%
Hypertensive			
Yes	8768	3474	28.4
No	7559	1011	11.8

*Stroke Buckle includes coastal plain region of North Carolina, South Carolina, and Georgia.

†Stroke Belt includes remainder of North Carolina, South Carolina, and Georgia, plus Alabama, Mississippi, Tennessee, Arkansas, and Louisiana.

impact on the likelihood of prevalent diabetes were race (30% in blacks vs 16% whites), income status (28% in lowest vs 15% in highest bracket), BMI category (10% normal vs 33% obese), physical activity status (26% never vs 19% any days of intense exercise), and hypertension status (28% hypertensive vs 12% nonhypertensive). Also of note is that prevalence of diabetes increased with increasing age category until age 74, then decreased in the 2 highest age categories, possibly indicative of higher mortality for those with diabetes.

Racial and Regional Variation in Diabetes

In white participants, the results of multivariable modeling adjusting for demographic factors revealed that residency in the Belt (OR, 1.22; 95% CI, 1.09, 1.36) and Buckle (OR, 1.26; 95% CI, 1.10, 1.44) was associated with increased risk for diabetes when compared to residency in the remainder of the United States (Table 2). Adjustment for SES resulted in only a slight reduction in the magnitude of this risk in both the Buckle and the Belt. Additional adjustment for risk factors further reduced this risk in the Belt (OR, 1.13; 95% CI, 1.00, 1.28) and Buckle (OR, 1.18; 95% CI, 1.01, 1.37). The addition of hypertension to the models had little effect on the magnitude of the associations, although for whites in the Buckle the difference no longer reached statistical significance (Table 2).

In black participants, after adjusting for demographic factors, residency in the Belt (OR, 1.13; 95% CI, 1.02, 1.26) and Buckle (OR, 1.45; 95% CI, 1.26, 1.66) was associated with increased risk for diabetes when compared to residency in the remainder of the United States (Table 2). Adjusting for SES reduced the odds among residents of the Belt to only 5% higher (OR, 1.05; 95% CI, 0.93, 1.17), a difference that was not statistically significant. In residents of the Buckle, adjusting for SES had minimal effect on the risk of diabetes, which remained a significant 38% greater than for residents in the remainder of the United States (OR, 1.38; 95% CI, 1.19, .59). These estimates changed minimally after additional adjustment for risk factors (OR, 1.34; 95% CI, 1.15, 1.57). The addition of hypertension to the model had no effect on the magnitude of the association in the Buckle (Table 2).

Awareness and Treatment of Diabetes and Control of Glucose Levels

Of the 4500 people with diabetes, 88.2% were aware that they had the disease, 95.7% of those aware were being treated, but only 56.1% of those being treated had their diabetes under control based on glucose level (Table 3). Multivariable

Table 2. ORs and 95% CIs for Diabetes by Region and Race

	Unadjusted	Demographic Adjusted*	Plus SES Adjusted†	Plus Risk Factor Adjusted‡	Plus Hypertension Adjusted§
White					
Stroke Buckle	1.21 (1.06, 1.39)	1.26 (1.10, 1.44)	1.21 (1.05, 1.40)	1.18 (1.01, 1.37)	1.15 (0.99, 1.34)
Stroke Belt	1.21 (1.09, 1.35)	1.22 (1.09, 1.36)	1.17 (1.04, 1.31)	1.13 (1.00, 1.28)	1.11 (0.97, 1.25)
Other regions	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Black					
Stroke Buckle	1.37 (1.20, 1.57)	1.45 (1.26, 1.66)	1.38 (1.19, 1.59)	1.34 (1.15, 1.57)	1.34 (1.15, 1.57)
Stroke Belt	1.10 (0.99, 1.22)	1.13 (1.02, 1.26)	1.05 (0.93, 1.17)	1.03 (0.91, 1.16)	1.01 (0.89, 1.14)
Other regions	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)

*Adjusts for demographics (age and gender).

†Adjusts for demographics plus SES (education, income, health insurance status).

‡Adjusts for demographics and SES plus risk factors (physical activity, BMI category, alcohol use, and smoking status).

§Adjusts for demographics, SES, risk factors, and hypertension status.

analyses revealed that there were no significant differences by region with regard to awareness and treatment of diabetes, or control of glucose levels, for either whites or blacks adjusting for demographic and SES factors (data not shown).

Discussion

This study confirms previous findings of both racial and geographic variation in the prevalence of diabetes with higher prevalence among blacks and southerners, suggesting that diabetes is a substantial contributor to the racial and geographic disparities in stroke mortality. Diabetes is significantly increased in both whites and blacks in the Buckle and the Belt compared to residents in the remainder of the United States. In black residents of the Belt, variations in SES, particularly education and income, appeared to explain much of the regional variations in diabetes. Whether there are other SES measures that are associated with prevalent diabetes and that might account for more of the association needs further exploration. Among black and white residents in the Buckle and whites in the Belt, regional differences were not fully mediated and remained significant when controlling for relevant risk factors. Addition of hypertension to these models did not explain this variation, suggesting that the increased risk in the region is not attributable to a single

subset of people having an increased “cluster” of risk factors including both diabetes and hypertension (that is, the increased risk in diabetes is “independent” of the increased risk in hypertension). The observed geographic variation in diabetes was also not explained by variation in awareness, treatment, or control of diabetes. As such, the reasons for this variation remain unclear, because it is unlikely that selective survival of those with diabetes in the regions where stroke mortality is highest explains the regional differences.

Whereas there are at least 10 hypothesized reasons for the existence of the Stroke Belt, perhaps the reason with the most national acceptance is a hypothesized excess of hypertension in the southeastern United States, which would contribute to a higher incidence of stroke.^{14,23,25–27} The acceptance of this hypothesis has contributed to the funding of studies that are attempting to “eliminate” the Stroke Belt primarily through improved blood pressure control in the region.²⁸ These analyses have shown that the observed regional variation in diabetes exists regardless of whether hypertension was included. Thus, it appears that regional variations in diabetes do follow a pattern similar to that observed for stroke mortality and that this variation is independent of hypertension status. These findings suggest that efforts directed at reducing diabetes in the Belt, and especially the Buckle, may be an

Table 3. Diabetes Awareness, Treatment, and Control by Region and Race

	Participants With Diabetes N (%)	Awareness (Among Those With Diabetes) N (%)	Treatment (Among Those Who Are Aware) N (%)	Control (Among Those Being Treated) N (%)
Total				
White	1945 (15.8)	1671 (85.9)	1578 (94.4)	862 (54.9)
Black	2550 (29.8)	2294 (89.9)	2217 (96.6)	1257 (57.0)
Buckle				
White	406 (16.9)	347 (85.5)	332 (95.7)	174 (52.4)
Black	415 (35.0)	377 (90.8)	368 (97.6)	199 (54.2)
Belt				
White	803 (16.8)	688 (85.7)	645 (93.8)	358 (55.8)
Black	791 (30.2)	717 (90.6)	687 (95.8)	380 (55.8)
Other regions				
White	736 (14.3)	635 (86.3)	600 (94.5)	329 (55.2)
Black	1344 (28.2)	1198 (89.1)	1160 (96.8)	676 (58.4)

important additional interventional strategy to reduce the disparity in stroke mortality associated with the Stroke Belt, especially because the combination of diabetes and hypertension may be more potent with regard to stroke risk and stroke mortality as compared to hypertension alone.

These findings also suggest that the prevalence of diabetes, but not the control of diabetes, is likely contributing to the geographic disparity in stroke mortality. Whereas this finding is currently true, the higher prevalence of obesity in the southern Stroke Belt region would seem to suggest that the geographic disparities in diabetes are likely to further increase, further fueling the geographic disparity in stroke. This adds further importance to reducing the geographic disparities in obesity.

The strengths and limitations of this study need to be mentioned. A limitation of these analyses is their cross-sectional nature and that they are not linked to risk of stroke. As with all epidemiological studies, participation rates also need to be considered. Because it is difficult to determine the eligibility of nonparticipants, the proportion of eligible subjects who participate is difficult to estimate. It has been conservatively estimated that $\approx 40\%$ of the eligible participants contacted have participated in the telephone interview,²⁹ which compares well with similar epidemiological studies. As is true in National Health and Nutrition Examination Survey (NHANES), this population is limited to noninstitutionalized individuals. The REGARDS cohort was not designed to be representative of the United States population because of over-sampling of blacks and residents of the Stroke Belt. Participants in REGARDS were required to have a telephone, which may further restrict the representativeness of the cohort; however, the recent report of Blumberg et al³⁰ estimates that among the target age group of REGARDS, 96% of individuals aged 45 to 64 and 98% of those older than age 65 have a land-line phone. Another possible limitation, which has been documented elsewhere,²⁴ is that the data at the in-home visit was collected by any of 6000 employees of Examination Management, Services, Inc. Although substantial training and visit standardization were attempted, those efforts cannot replicate the quality of a smaller clinic-based staff. This limitation is partially offset by advantages of a true nationally based large sample in which participants were assessed in their homes. In addition, because this report is based on a partial sample (21 959 of 30 000 participants) there could be a potential for temporal change; however, because the participants are being randomly selected (from 12 strata; 3 regions \times 2 races \times 2 sexes) there is no reason to assume that results from this partial sample will differ from the entire cohort. There was no evidence of temporal change in the age-race-sex adjusted rates of diabetes or hypertension.

Other limitations relate to establishing diabetes status. First, it was not possible to separate type 1 from type 2 diabetes. Second, we use only 1 assessment of glucose to establish diabetes status compared to the standard clinical definition that requires 2 assessments and as such this could contribute to "over-diagnosis" (by the clinical definition) of diabetes in this article; however, the definition used here is quite standard in epidemiological studies, mainly because it is impractical to ask volunteers to return to a clinic visit (or in

the case of REGARDS to perform 2 in-home assessments). Third, glucose measurements are missing on 928 participants. These data were missing for 2 reasons: (1) delays in blood shipment so that the glucose assay would be biased and (2) a minor number were not available because the assays were currently being processed in the central laboratory and results were not transferred to the data center. The likelihood that either of these causes would occur is not related to diabetes status or region of the country. Any missing data are "missing at random" and the presence/absence of individual data items should not affect results.

A final limitation relates to definitions of diabetes treatment and control. As is common in other studies, we defined "treatment" of diabetes as the self-reported use of medications. It is possible that some participants with diabetes were on nondrug interventions (diet, weight loss, exercise, or the like) and would not be classified as having diabetes. With respect to diabetes control, hemoglobin A1C values, the preferred method for estimating diabetes control, were not available. As such, estimates of control had to be made using blood glucose levels which are known to be less precise.

A strength of the study is that determination of disease status did not solely depend on self-report. Previous studies, such as the Behavioral Risk Factor Surveillance System, used self-reported diabetes alone, which can result in substantial misclassification and which could differ by region and race/ethnicity, leading to spurious differences by these factors. An additional strength of REGARDS is that the current analyses consisting of $>20\,000$ participants is almost 4-times the size of the 5448 available in NHANES III,²³ thus yielding more precise estimates of rates of diabetes and diabetes awareness, treatment, and control. For instance, if we compare diabetes prevalence and diabetes awareness (using the same definition of awareness) in non-Hispanic white participants aged 60 and older in REGARDS to the same race and age group in NHANES, we find higher prevalence of diabetes (22.8% REGARDS vs 16.5% NHANES) and diabetes awareness (87.0% REGARDS vs 65.3% NHANES) in the REGARDS cohort, suggesting that NHANES may be underestimating the prevalence of diabetes and the associated magnitude of its effect on geographic disparities in stroke mortality.³¹

In summary, these analyses support a possible role of regional variation in diabetes as in part an explanation for the regional variation in stroke mortality, and more importantly suggest that there may be unique factors present in the Buckle and Belt that lead to an increased risk of diabetes more than that which can be explained by regional variation in the standard risk factors for diabetes. With the obesity epidemic particularly in states in the southeastern United States, the contribution of diabetes to the geographic disparity in stroke mortality will likely grow. Without intervention to reduce the impact of diabetes, unfortunately, these findings may portend an increasing disparity of stroke in the southeastern United States.

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