Incident Cognitive Impairment is Elevated in the Stroke Belt: The REGARDS Study

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Objective: To determine whether incidence of impaired cognitive screening status is higher in the southern Stroke Belt region of the United States than in the remaining United States.
Methods: A national cohort of adults age $\geq$45 years was recruited by the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study from 2003 to 2007. Participants' global cognitive status was assessed annually by telephone with the Six-Item Screener (SIS) and every 2 years with fluency and recall tasks. Participants who reported no stroke history and who were cognitively intact at enrollment (SIS $>$4 of 6) were included (N = 23,913, including 56% women; 38% African Americans and 62% European Americans; 56% Stroke Belt residents and 44% from the remaining contiguous United States and the District of Columbia). Regional differences in incident cognitive impairment (SIS score $\leq$4) were adjusted for age, sex, race, education, and time between first and last assessments.
Results: A total of 1,937 participants (8.1%) declined to an SIS score $\leq$4 at their most recent assessment, over a mean of 4.1 ($\pm$1.6) years. Residents of the Stroke Belt had greater adjusted odds of incident cognitive impairment than non-Belt residents (odds ratio, 1.18; 95% confidence interval, 1.07–1.30). All demographic factors and time independently predicted impairment.
Interpretation: Regional disparities in cognitive decline mirror regional disparities in stroke mortality, suggesting shared risk factors for these adverse outcomes. Efforts to promote cerebrovascular and cognitive health should be directed to the Stroke Belt.

ANN NEUROL 2011;00:000–000

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is an epidemiological study following a cohort of US adults for stroke and cognitive decline. In reports from REGARDS, self-reported stroke symptoms in the absence of diagnosed stroke were considered as potential markers of ischemic changes. Such symptoms, reported by 18% of REGARDS participants,[1] were associated with a 24% increased risk of prevalent cognitive impairment after controlling for age, sex, race, education, and region of residence.[2] Decrements in cognitive function may serve in some cases as a proxy for unrecognized small strokes,[2] a notion that is supported by demonstrated associations between magnetic resonance imaging-defined silent brain infarcts, cognitive deficits, and incident dementia.[3–7] It is not known, however, whether incidence of cognitive impairment is elevated in the Stroke Belt region of the United States, a region of the southeastern United States first described in 1965 as having 50% higher stroke mortality rates than the remaining United States.[8] Centers for Disease Control and Prevention state statistics from 2000 to 2006 reveal that among adults aged 35 years and older, age-adjusted annual rates of stroke mortality in the 8 Stroke Belt states were, on average, 125 per 100,000, compared to an average rate of 96 per 100,000 in the remaining 40 contiguous states and the District of Columbia.[9] During the same period, age-adjusted stroke hospitalization rates among Medicare beneficiaries aged 65 years and older followed a similar pattern of higher concentration in the Stroke Belt.[9]

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.22432

Received Feb 13, 2011, and in revised form Mar 16, 2011. Accepted for publication Mar 18, 2011.

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It is plausible that incidence of cognitive impairment might be elevated in the Stroke Belt due to subclinical strokes and cerebrovascular disease as well as to precursor or concomitant risk factors for both stroke and cognitive impairment, such as hypertension, diabetes, kidney disease, and metabolic syndrome.[10–16] The purpose of the present analysis from the REGARDS study was to examine incident impairment in cognitive screening status in the southern Stroke Belt region relative to the remaining 40 contiguous states. Among participants who had intact cognitive screening status at baseline and no history of stroke, we predicted regional differences in incident cognitive impairment that reflect well-documented regional differences in stroke incidence and mortality. Specifically, we hypothesized that there would be greater occurrence of incident impairment in cognitive screening performance in the Stroke Belt relative to the rest of the United States.

Subjects and Methods

Design and Procedures

Designed to determine the causes of higher stroke mortality among African Americans (AAs) and residents of the Stroke Belt, the REGARDS study included only AAs and European Americans (EAs). Using mail and telephone contact methods, participants were recruited from January 2003 to October 2007 from lists of US residents purchased from Genesys (Daly City, CA). Genesys lists include >100 million US households from InfoUSA List Install and Experian Insource consumer databases, which in turn draw from multiple sources, including telephone directories, automobile and motorcycle registrations, real estate listings, and driver's license data. The lists were stratified with respect to age, race, sex, and geographic region to accommodate the REGARDS sampling strategy.[17] The cohort consists of 30,239 US residents aged ≥45 years, with 16,934 from Stroke Belt states (Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Tennessee) and 13,305 from the remaining 40 contiguous states and the District of Columbia (collectively, the non-Belt). A modification of standardized methods recommended by Morton and colleagues[18] was used to determine telephone participation rates in REGARDS, with an adjustment for telephone numbers called <15×. The cooperation rate was 49%; this calculation represents the number of recruited participants divided by all potential participants for whom eligibility was confirmed. The response rate was 33%; this calculation includes an additional adjustment for potential participants who were estimated likely to have been eligible but whose eligibility could not be confirmed.

Participants answered demographic and medical history questions during a computer-assisted telephone interview conducted by the Survey Research Unit at the University of Alabama at Birmingham. During a home visit conducted by Examination Management Services, anthropometric measurements, blood and urine, and an electrocardiogram were obtained. Participants were followed by telephone twice per year to gather information on hospitalized events. When suspected incident stroke events were reported during follow-up calls, medical records were obtained and adjudicated by study physicians.

A baseline telephone cognitive screener was first administered to REGARDS participants in December 2003, 11 months after study enrollment began. Subsequently, it was administered to all participants annually. An expanded cognitive battery including list learning and recall and verbal fluency assessment was implemented in 2006 and conducted during follow-up calls at 2-year intervals.

The REGARDS study was approved by the institutional review boards of all participating institutions. Written informed consent was obtained from all participants.

Participants

For the present analyses, participants were excluded if they reported a history of stroke at baseline, if they had impaired cognitive status at first assessment, or if they lacked at least 2 cognitive screening assessments. Any cognitive data obtained after the date of a confirmed incident stroke were censored.

Measures

Age, sex, race, educational attainment, and state of residence were assessed by self report. Age was a continuous variable calculated from birth date. Race was categorized as AA or EA. Educational attainment was categorized as less than high school, high school graduate, some college or vocational training, or college graduate. States of residence were classified as belonging to the Stroke Belt or non-Belt.

The main outcome for the present analyses was incident cognitive impairment as defined by each participant's most recent score on the Six-Item Screener (SIS).[19] Designed for either in-person or telephone administration, the SIS is a test of global cognitive function derived from the widely used Mini-Mental State Exam (MMSE).[20] Items assess recall of a 3-item word list and temporal orientation (year, month, day of the week). The upper limit of reliability for the SIS may be presumed to be capped by the test–retest reliability of the MMSE (0.80–0.95 for both cognitively intact and impaired adults in the absence of illness-induced changes[21]). In a prior study, the SIS was validated against the MMSE, list learning tasks, and diagnoses of dementia and cognitive impairment-no dementia (CIND) in a community sample of 344 AA adults and an ethnically diverse clinical sample of 651 adults.[19] Both samples underwent a second-stage formal diagnostic evaluation. Scores on the SIS range from 0 to 6. In community samples, a score of 4 or fewer correct indicates cognitive impairment[19,22,23] with 74.2% sensitivity and 80.2% specificity for clinically confirmed CIND and dementia.[19]

Incident cognitive impairment was defined as a shift from intact cognitive screening status (score of 5 or 6 correct) at the first assessment to impaired cognitive screening status (score of 4 or fewer correct) at the latest available assessment. A

more stringent definition of incident impairment, in which a score in the impaired range was required at the 2 latest assessments, was also evaluated.

From the expanded cognitive battery, scores from participants' first assessments of semantic fluency and word list recall were inspected to determine whether scores on these measures differed as a function of SIS incident impairment classifications. Scores on semantic fluency consist of the number of animals generated in 1 minute.[24,25] Recall scores from the Consortium to Establish a Registry for Alzheimer's Disease Word List[24] consist of the number of words recalled (0–10) after a delay following 3 learning trials.

Statistical Approach

Analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC).

REGIONAL ANALYSES. Because the SIS was validated using dichotomous outcomes rather than continuous scores,[19,22] logistic regression was selected to assess the probability of being impaired at the most recent available assessment. Regional disparities in incident cognitive impairment were examined by comparing the Stroke Belt and non-Belt after multivariate adjustment for age, race, sex, and educational attainment, as well as the time interval between each participant's first and most recent assessment, which varied depending upon the date of enrollment. Sensitivity analyses with impaired scores at the 2 most recent assessments used a similar approach. Odds ratios (ORs) and 95% confidence intervals (CIs) were generated from the regression models. Survival analyses using proportional hazards models were also conducted to determine whether censoring cases following the first occurrence of an SIS score indicative of cognitive impairment would produce different results than the regression approach in which we considered only the most recent assessments for capturing incident cognitive impairment. Finally, participants' initial semantic fluency and delay recall scores were examined using general linear models in which SIS impairment classification and region of residence were predictors, and age, race, sex, and education level were covariates.

STATE-SPECIFIC ANALYSES. The percentage of participants who met criteria for incident impairment in each state was first inspected relative to the national mean percentage obtained in REGARDS. Then, logistic regression was used to compare adjusted odds of incident impairment among states with sufficient numbers of participants. For a sample of 100 participants, the margin of error (95% CI) surrounding estimates approached 5%, suggesting likely instability in estimates based on smaller samples. Therefore, a minimum of 100 participants within each state was set as the threshold for inclusion in these state-specific analyses. Adjusted ORs were generated using the last state entered into analysis as the default reference value. The ORs were then rank ordered, and the ranked distribution was split dichotomously for illustrative purposes.

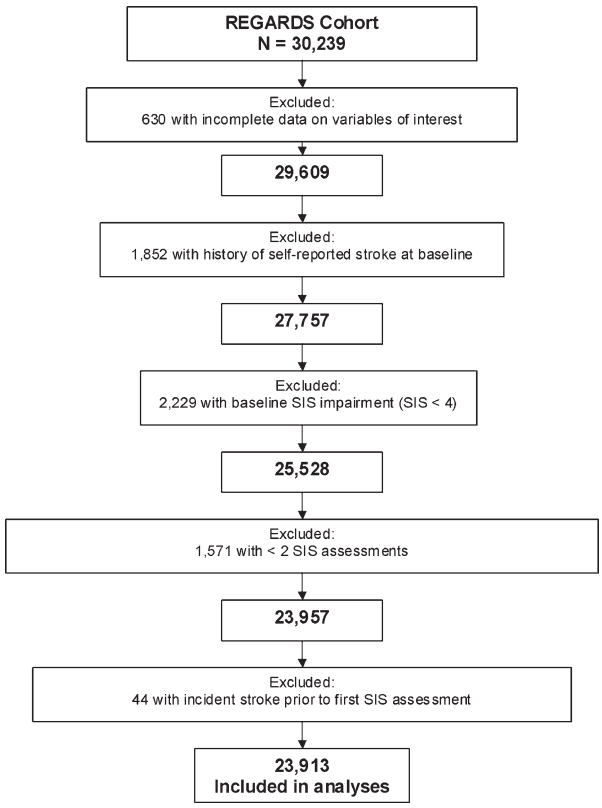

FIGURE 1: Participants available for analyses of incident cognitive impairment. SIS = Six-Item Screener.

Results

Analyses for this report were based on data acquired through October 1, 2010. Figure 1 portrays the steps involved in obtaining the analytic sample of 23,913 participants from the full REGARDS cohort. Descriptive characteristics of this sample, overall and by region of residence, appear in Table 1.

Of the 23,913 participants, 1,937 (8.1%) scored in the range of impaired cognitive status at their most recent assessment, over intervals ranging from 1 to 7 years (mean $= 4.1 \pm 1.6$ years) following the initial assessment.

Regional Results

In multivariate analyses, Stroke Belt residents had higher odds of incident cognitive impairment than non-Belt residents (OR, 1.18; 95% CI, 1.07–1.30); all demographic factors and time also independently predicted incident impairment (Table 2). A 10-year increment in age, AA race, and educational attainment less than high school completion were associated with considerably stronger odds of incident impairment (ORs >2) than was region of residence. In the sensitivity analyses of those with impaired scores at the 2 most recent assessments (438 of the 23,913 participants), results were similar but with larger ORs, suggesting stronger relationships between

TABLE 1: Characteristics of Included Participants

Characteristic	All, N = 23,913	Stroke Belt, n = 13,303[a]	Non-Belt, n = 10,610[b]
Stroke Belt resident	13,303 (56%)	n/a	n/a
Age, yr, mean ± SD	64.2 ± 9.2	63.7 ± 9.1	64.9 ± 9.3
African American	9,046 (38%)	4,595 (35%)	4,451 (42%)
Women	13,486 (56%)	7,770 (58%)	5,716 (54%)
Education, n = 23, 901; missing = 12			
Less than high school	2,394 (10%)	1,523 (11%)	871 (8%)
High school graduate	6,027 (25%)	3,515 (26%)	2,512 (24%)
Some college	6,508 (27%)	3,548 (27%)	2,960 (28%)
College graduate	8,972 (38%)	4,713 (35%)	4,259 (40%)
Assessment interval, yr, mean ± SD	4.1 ± 1.6	4.0 ± 1.6	4.3 ± 1.6

[a]Stroke Belt states include Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Tennessee.
[b]Non-Belt states include all 40 remaining contiguous United States and the District of Columbia.
n/a = not applicable; SD = standard deviation.

each variable and the odds of cognitive impairment (Table 3).

Results of proportional hazards models were fully consistent with the logistic regression approach with respect to the direction, magnitude of regression coefficients, and significance of results (data not shown).

Among those participants who had initial assessments of semantic fluency (n = 13,462) and delay recall (n = 17,500) in 2006 or later, covariate-adjusted scores on each differed by incident impairment classification and region of residence. For semantic fluency, adjusted mean scores were lower for participants with incident impairment than without, $F_{8,\ 13,448} = 67.15$, $p < 0.0001$, and for residents of the Stroke Belt versus the remaining United States, $F_{8,\ 13,448} = 126.81$, $p < 0.0001$. Similarly, delay recall adjusted mean scores were significantly lower for those with incident impairment, $F_{8,\ 17,483} = 275.64$, $p < 0.0001$, and for Stroke Belt residents, $F_{8,\ 17,483} = 39.35$, $p < 0.0001$.

State-Specific Results

Twenty-two non-Belt states, the District of Columbia (DC), and all 8 Stroke Belt states had >100 eligible REGARDS participants, ranging from 102 in Washington

TABLE 2: Multivariate Odds Ratios for Incident Cognitive Impairment at Most Recent Assessment (1,937 of 23,913 Participants) by Region, Demographics, and Time between First and Last Assessments

Effect	Adjusted Odds Ratio Estimates		
	Point Estimate	95% Confidence Limits	
Stroke Belt vs non-Belt states	1.18	1.07	1.30
Age in 10-year increments	2.09	1.98	2.20
Race (AA vs EA)	2.09	1.89	2.31
Sex (women vs men)	0.65	0.59	0.72
Education			
Less than high school vs college grad	2.27	1.96	2.64
High school grad vs college grad	1.55	1.36	1.76
Some college vs college grad	1.14	1.00	1.31
Time interval in 1-year increments	0.92	0.89	0.95

All odds ratios in the multivariate model are adjusted for each of the other variables shown in the table.
AA = African American; EA = European American.

TABLE 3: Multivariate Odds Ratios for Incident Cognitive Impairment at 2 Most Recent Assessments (438 of 23,913 Participants) by Region, Demographics, and Time between First and Last Assessments

Effect	Adjusted Odds Ratio Estimates		
	Point Estimate	95% Confidence Limits	
Stroke Belt vs non-Belt states	1.40	1.15	1.72
Age in 10-year increments	3.07	2.74	3.45
Race (AA vs EA)	2.74	2.23	3.38
Sex (women vs men)	0.64	0.53	0.78
Education			
Less than high school vs college grad	2.80	2.11	3.71
High school grad vs college grad	1.64	1.24	2.16
Some college vs college grad	1.32	0.99	1.76
Time interval in 1-year increments	1.15	1.09	1.22

All odds ratios in the multivariate model are adjusted for each of the other variables shown in the table.
AA = African American; EA = European American.

to 2,814 in North Carolina. There were a total of 23,298 participants included in the state-specific analyses. Six of the 8 (75%) Stroke Belt states had a higher percentage of participants with incident cognitive impairment than the national mean of 8.1%, compared to 10 of 23 (43.5%) non-Belt states, including DC.

Figure 2 displays the state-by-state pattern of incident cognitive impairment resulting from the rank ordered multivariate ORs. The obtained distribution of ORs was split dichotomously. Participants in the 16 states with dark shading were in the half of the OR distribution at higher risk for incident impairment, whereas cohorts in the 15 states with light shading were in the half at relatively lower risk. Because statistical significance is a function of both the magnitude of the effect and the sample size within each state, the figure depicts the pattern of results only, irrespective of the significance level of each OR.

Discussion

Incident cognitive impairment occurred, over an average interval of 4 years, among 8.1% of US adults aged 45 years and older in this study. The odds of incident cognitive impairment were 18% higher among residents of the Stroke Belt than among non-Belt residents after adjusting for strong independent predictors of cognitive decline, including age, sex, and education level. When impairment at the 2 most recent consecutive assessments was required for incident case definition, the adjusted odds increased to 40% higher risk in the Stroke Belt region, suggesting an even greater regional disparity in persisting impairment. This study is the first known documentation of higher incident cognitive impairment in the Stroke Belt region of the United States than in the rest of the nation.

The higher adjusted incidence of impairment among Stroke Belt residents also remained after

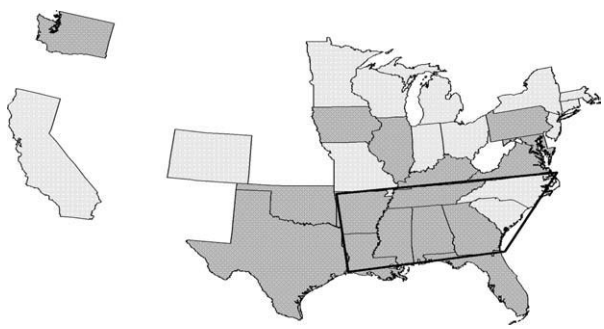

FIGURE 2: State-specific map of incident cognitive impairment (n = 23,298). The map depicts dichotomously split ranked odds of state-specific incident cognitive impairment, adjusted for age, race, sex, education level, and time between first and last cognitive assessments. In the median split of the distribution of odd ratios, lightly shaded states (rank 1) had lower ranked odds of incident impairment. Darkly shaded states (rank 2) had higher odds. Unshaded states had insufficient data for inclusion (states with <100 eligible participants: Arizona, Delaware, Idaho, Kansas, Maine, Montana, Nebraska, Nevada, New Hampshire, New Mexico, North Dakota, Oregon, Rhode Island, South Dakota, Utah, Vermont, West Virginia, and Wyoming). The Stroke Belt states are outlined.

controlling for the significant association with race, thereby obviating the potential confounding of race with region. Historically, there has been a greater concentration of AA adults living in the Stroke Belt than in the remaining United States,[26] and living in the Stroke Belt and being AA both increase risk for stroke mortality. The excess stroke mortality borne by AAs appears to be due to higher stroke incidence rates among AAs, which is particularly apparent at younger ages.[26–29] The same factors that increase risk for stroke—hypertension, diabetes, kidney disease, and metabolic syndrome—also increase risk for cognitive impairment.[10–16] With the exception of kidney disease,[16] these conditions disproportionately affect AA adults.

Incident impairment based on SIS performance was robustly associated with well-established risk factors for cognitive decline, including older age and fewer years of education. Using the SIS, we found approximately 2% incident impairment annually—somewhat lower than annual incidence rates reported by studies that used clinical diagnostic assessments for dementia (3.2%)[30] and mild cognitive impairment (5.1%),[31] likely due in part to the younger mean age of our cohort. In addition, practice effects among those with opportunity for multiple annual exposures to the SIS might have served to lower detection of subtle impairment.[32] Our relatively low annualized percentage of incident impairment is consistent with a report demonstrating in 2 independent population-based cohorts that estimated declines in cognitive function are smaller, irrespective of statistical approach, when using long (eg, 5-year) compared to short (eg, 1-year) follow-up periods, due to health and survival effects that bias longer follow-up periods (eg, selective attrition of participants with lower levels of cognitive function).[33] The net impact of such processes would be underestimation of incident impairment.

Inspection of the geographic patterns of cognitive impairment reveals a preponderance of incident cases among participants throughout the South, extending from the East Coast to Texas and Oklahoma in a pattern that is generally concordant with shifting stroke mortality patterns, which have spread toward the Mississippi River Valley and westward within the past 50 years.[34] Casper and colleagues have suggested that the changing geographic pattern of stroke mortality may reflect geographic changes in economic resources that are associated with patterns of medical and behavioral risk factors, migration patterns, and health care standards.[34] It is plausible that these same factors influence trajectories of cognitive function.

The findings of this study are subject to limitations. First, the SIS used to assess cognitive status likely lacks sensitivity to subtle cognitive changes. Even so, our documentation of clear regional differences in the probability of cognitive decline provides evidence that the screener is sufficiently sensitive for epidemiological research. We confirmed our SIS findings using 2 statistical methods and 2 definitions of incident impairment. Our incident impairment classifications coincided with lower performance on 2 more sensitive measures of cognitive function, and adjusted scores on these additional measures were lower in the Stroke Belt than in the rest of the nation, providing corroboration of geographic variations in incident cognitive impairment. Previous findings from REGARDS attest to the utility of the SIS in detecting broad patterns of association with conditions affecting cognition, such as traditional cardiovascular risk factors,[2,35,36] chronic kidney disease,[16] and congestive heart failure.[37]

A second limitation is that our cooperation and response rates are moderate, although comparable to those achieved by similar population-based studies. These rates leave open the possibility that nonresponse bias could affect interpretation of our results. In addition, a large block of the western United States was not included in the state-level analyses. The small number of REGARDS participants in those states—a product of simple random sampling, which selects fewer participants from states that are relatively sparsely populated—was deemed insufficient to provide stable estimates of incident decline. Participants in these states were, however, included in the primary analysis of regional differences. Additionally, although we employed a random sampling strategy, cohorts of participants in the state-level analyses may not be representative of the states as a whole.

Future work should examine the influence of migration patterns, urban/rural residence, life course socioeconomic factors, and educational quality in relation to cognitive decline, as well as proximate causes of incident cognitive impairment. Earlier work by our group suggests several likely cardiovascular and stroke risk factors to pursue.[2,35,36] Pinpointing regional patterns in the contribution of modifiable risk factors to incident cognitive impairment will allow for geographically concentrated prevention and intervention efforts.

Such efforts will be particularly important for those segments of the population who are most vulnerable to incident impairment. The information gained by tracking the physical and cognitive health of the REGARDS cohort of >12,000 AA and >18,000 EA adults may be used to design and implement appropriate programs and services for older Americans at both state and national levels.

Acknowledgments

This research project is supported by a cooperative agreement U01 NS041588 from the National Institute of

Neurological Disorders and Stroke, NIH, Department of Health and Human Services. Additional funding was provided by the Centers for Disease Control and Prevention's Healthy Aging Program. The content is solely the responsibility of the authors and does not necessarily represent the official views and positions of the National Institute of Neurological Disorders and Stroke, the NIH, or the Centers for Disease Control and Prevention. Representatives of the funding agencies were involved in the review of the manuscript prior to submission for publication.

We thank the other investigators, the staff, and the participants of the REGARDS study for their valuable contributions. A full list of participating REGARDS investigators and institutions can be found at http://www.regardsstudy.org.

Potential Conflicts of Interest

R.G.: travel support, NIH. B.K.: consultancy and travel support, Allergan. L.A.M.: travel support, NIH.

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