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Journal
Neurology, 80(18)

ISSN
0028-3878

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Publication Date
2013-04-30

DOI
10.1212/wnl.0b013e3182904d59

Peer reviewed

Effect of duration and age at exposure to the Stroke Belt on incident stroke in adulthood

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ABSTRACT

Objective: To assess whether there are differences in the strength of association with incident stroke for specific periods of life in the Stroke Belt (SB).

Methods: The risk of stroke was studied in 24,544 black and white stroke-free participants, aged 45+, in the Reasons for Geographic and Racial Differences in Stroke study, a national population-based cohort enrolled 2003–2007. Incident stroke was defined as first occurrence of stroke over an average 5.8 years of follow-up. Residential histories (city/state) were obtained by questionnaire. SB exposure was quantified by combinations of SB birthplace and current residence and proportion of years in SB during discrete age categories (0–12, 13–18, 19–30, 31–45, last 20 years) and entire life. Proportional hazards models were used to establish association of incident stroke with indices of exposure to SB, adjusted for demographic, socioeconomic (SES), and stroke risk factors.

Results: In the demographic and SES models, risk of stroke was significantly associated with proportion of life in the SB and with all other exposure periods except birth, ages 31–45, and current residence. The strongest association was for the proportion of the entire life in SB. After adjustment for risk factors, the risk of stroke remained significantly associated only with proportion of residence in SB in adolescence (hazard ratio 1.17, 95% confidence interval 1.00–1.37).

Conclusions: Childhood emerged as the most important period of vulnerability to SB residence as a predictor of future stroke. Improvement in childhood health circumstances should be considered as part of long-term health improvement strategies in the SB. *Neurology*® 2013;80:1655–1661

GLOSSARY

CATI = computer-assisted telephone interview; **CI** = confidence interval; **ECG** = electrocardiogram; **FSRS** = Framingham Stroke Risk Score; **HR** = hazard ratio; **LVH** = left ventricular hypertrophy; **MI** = myocardial infarction; **REGARDS** = Reasons for Geographic and Racial Differences in Stroke; **SB** = Stroke Belt; **SBP** = systolic blood pressure; **SES** = socioeconomic status.

The Stroke Belt region (SB) in the southeastern United States has higher stroke mortality than the rest of the United States,[1,2] and national data suggest that similar regional differences exist in stroke incidence.[3–6] There are several hypothesized reasons for this but data for testing the underlying factors are limited.[2] Research to date has shown that only a portion of the higher stroke mortality can be explained by traditional risk factors.[7–10] SB has been defined using state of residence at time of death. Population migration may contribute to differences in regional mortality rates but few US studies have considered the impact of population redistribution on geographic disparities in stroke incidence and mortality.[11–14] Some,[12–14] but not all,[11] studies have shown that birthplace is associated with cardiovascular mortality, with individuals born in the Southeast having higher rates than those born in other regions of the United States. With respect to stroke incidence, one national study showed increased incidence of self-reported stroke associated with living in the SB during childhood.[6]

It is not known whether there is a "sensitive period" for residence in the SB, i.e., a developmental period during which SB exposure has the greatest consequences for later stroke risk, or whether stroke risk accumulates with each additional year of residence in the SB.[15] We use lifetime residential history

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

data from a national US cohort to examine the associations of duration of and age at exposure to the SB with incidence of physician-adjudicated stroke.

METHODS The Reasons for Geographic and Racial Differences in Stroke (REGARDS) is a population-based national cohort study of 30,239 community-dwelling individuals, aged 45 or older at enrollment in 2003–2007. Twenty-one percent of the sample was randomly selected from current residence in the "buckle" of the SB[16] (coastal plain region of North Carolina, South Carolina, and Georgia), 35% from the rest of the SB states[17] (the remainder of North Carolina, South Carolina, and Georgia plus Alabama, Mississippi, Tennessee, Arkansas, and Louisiana), and the remaining 44% from the other 40 contiguous states. A US map showing distribution of participants' state of residence at time of enrollment is provided elsewhere.[5] Individuals were identified from commercially available lists of residents, and contacted by mail followed by telephone. Using a computer-assisted telephone interview (CATI), trained interviewers obtained demographics, medical history, and lifestyle factors including an array of potential risk factors. A brief physical examination including blood pressure measurements, blood and urine samples, anthropometry, and an electrocardiogram (ECG) was conducted in-person 3–4 weeks after the CATI. Follow-up is every 6 months by telephone for self-reported suspected stroke (or proxy-reported in case of death or small number of participants unable to respond), with retrieval of medical records and adjudication by physicians. Additional methodologic details are provided elsewhere.[5,18]

Standard protocol approvals, registrations, and participant consents. Consent was obtained verbally by phone and later in writing during the in-person evaluation. The institutional review boards of participating institutions approved the study methods.

Age and duration of exposure to the SB. During the in-person assessment, self-administered questionnaires were left with the participant to be returned by self-addressed prepaid envelopes. Questionnaires included residential history information recording city/state (or country) of birth, every city/state where participant had lived for at least 1 year, and age at which he or she moved from each location. Detailed methods of coding and classification of age at exposure and years of exposure to city/state in the SB are described elsewhere.[19] Briefly, each questionnaire was processed into individual records containing city/state at birth and if applicable, any relocation. Records with valid state names were matched using US Census Bureau Federal Information Processing Standards codes for states and counties, and named populated places were used to confirm all city/state listings.[20] SB exposure was quantified by 8 indices: birth in SB, current SB residence, and proportion of years in SB during the first 12 years, ages 13–18, ages 19–30, ages 31–45, the last 20 years, and entire life. These categories were chosen to correspond to traditional cutpoints of life periods.

Covariates. Variables in the Framingham Stroke Risk Score (FSRS) were used as covariates (i.e., age, sex, systolic blood pressure [SBP], use of antihypertensive medications, current smoking, history of heart disease, diabetes, left ventricular hypertrophy [LVH], and atrial fibrillation) as well as adult socioeconomic status (SES) (defined by annual household income and education). Age, race, sex, use of antihypertensive therapy, smoking (current vs not), annual family income ($<$ or $\geq$ \$20,000/year), and education level ($<$ high school vs $\geq$ high school graduate) were defined by self-report. SBP was defined as the average of 2 measurements taken by a trained technician using a standard protocol, after the participant was seated for 5 minutes. History of heart disease was defined as self-reported myocardial infarction (MI), coronary artery bypass surgery, coronary angioplasty or stenting, or evidence of MI from ECG. Diabetes was defined as fasting glucose level $\geq$126 mL/dL (or $\geq$200 mL/dL if participant was nonfasting), or self-reported medication use for glucose control. LVH was defined by centrally read ECG. Atrial fibrillation was defined by self-report or ECG.

Stroke events determination. Methods of stroke adjudication are reported elsewhere.[5] Briefly, during CATI follow-up, a report of possible stroke, TIA, death, hospitalization, or emergency department visit for brain aneurysm, brain hemorrhage, stroke symptoms, or unknown reason generated a request for retrieval of medical records. Following initial review by a stroke nurse to exclude obvious nonstroke, medical records of suspected strokes were centrally adjudicated by physicians. For deaths with no medical records, death certificates or proxy interviews were adjudicated. Stroke events were defined following the WHO definition.[21] Events not meeting the WHO definition but with symptoms lasting $>$24 hours with neuroimaging consistent with acute ischemia or hemorrhage were classified as "clinical strokes." "Probable stroke" was classified when adjudicators agreed that the event was likely a stroke but information was insufficient to meet other classifications. This analysis included WHO-defined, clinical, and probable stroke cases, and both ischemic and hemorrhagic strokes.

Statistical analyses. Demographic data were described as mean (SD) and n (%) as appropriate, overall and by a variable describing place of birth and current residence as either in or out of the SB. Cox proportional hazards analysis was used to examine hazard ratios (HR) and 95% confidence intervals (CI) for incident stroke associated with SB exposure periods. In addition, we assessed the impact of the combination of birth residence and current residence in the SB (4 strata) on the risk of stroke. Models were adjusted for age, sex, and race (demographic model), further adjusted for SES, and then for components of the FSRS. Although time periods of living in the SB are correlated, the main goal of analysis was to assess if there are differences in the strength of association with incident stroke for specific periods of life in the SB, addressing the question of whether living in the SB at a particular age period imparts greater stroke risk than living there at other age periods. For each possible pairwise combination of SB exposure periods, bootstrapping was used to calculate p values for the test of differences in the strength of association.

Given the differential historical migration patterns for black and white people,[22,23] race-stratified analyses were conducted, adjusting for age and sex. Because of missing stroke data due to ongoing adjudication and differential retrieval of medical records, we applied multiple imputation techniques to classify potential stroke events using a logistic function predicting the likelihood that an attempted record retrieval would result in an adjudicated stroke.[24]

The analysis cohort comprised 24,544 participants, excluding those with no follow-up (2%), self-reported stroke at baseline (6%), missing residential questionnaire (8%), and place of birth missing or out of the United States (2%). The end of follow-up for analysis was April 1, 2011, resulting in 141,736 person-years of follow-up.

RESULTS Overall, 39% of the participants were black, 56% were women, mean age at time of enrollment was 64.8 years (SD 9.3), and the sample overall had lived 51% of their lives in the SB (table 1). Of those who were born in the SB and also lived there at study enrollment, on average 95% of their life had been spent in the SB. For those who were not born in the SB but lived there at time of enrollment, the average proportion of their life spent in the SB was 54%. Of those who were born in the SB and lived outside the region at enrollment, the average proportion of time lived in the SB was 23%, and for

Table 1 Characteristics of the study population by birthplace and current residence in Stroke Belt

	Total cohort (n = 24,544)	Born and current residence in SB (n = 10,626)	Born in SB, current residence outside SB (n = 2,109)	Not born in SB, current residence in SB (n = 3,294)	Not born in SB and current residence outside SB (n = 8,515)
Age, y, mean ± SD	64.8 ± 9.3	64.2 ± 9.2	66.5 ± 8.7	64.2 ± 9.1	65.3 ± 9.6
Black race, n (%)	9,535 (39)	4,545 (43)	1,814 (86)	491 (15)	2,685 (32)
Male, n (%)	10,761 (44)	4,199 (40)	867 (22)	1,608 (49)	4,087 (48)
Household income <$20,000, n (%)	4,132 (17)	2,237 (21)	472 (22)	331 (10)	1,092 (13)
Educational level < high school diploma, n (%)	2,744 (11)	1,615 (15)	405 (19)	164 (5)	560 (7)
Proportion of life in SB, mean ± SD	0.51 ± 0.45	0.95 ± 0.13	0.23 ± 0.16	0.54 ± 0.30	0.01 ± 0.04
Variables in the Framingham Stroke Risk Score					
Taking hypertensive medications, n (%)	12,224 (52)	5,630 (55)	1,279 (63)	1,460 (46)	3,855 (47)
Systolic blood pressure, mm Hg, mean ± SD	127.1 ± 16.3	127.4 ± 16.4	130.5 ± 17.5	125.1 ± 15.8	126.5 ± 16.0
History of heart disease, n (%)[a]	4,045 (17)	1,783 (17)	349 (17)	515 (16)	1,396 (17)
Diabetes mellitus, n (%)	4,821 (20)	2,388 (23)	546 (27)	519 (16)	1,368 (17)
Left ventricular hypertrophy (by ECG evidence), n (%)	2,270 (9)	1,025 (10)	293 (14)	219 (7)	733 (9)
Atrial fibrillation (by self-report or ECG evidence), n (%)	1,992 (8)	901 (9)	152 (7)	279 (9)	660 (8)
Current smoker, n (%)	3,409 (14)	1,524 (14)	322 (15)	442 (13)	1,121 (13)

Abbreviations: ECG = echocardiography; SB = Stroke Belt.
[a] History of heart disease defined as self-reported myocardial infarction, coronary bypass surgery, coronary angioplasty/stenting, or evidence of myocardial infarction on ECG.

persons not born there and not living there at enrollment, their average exposure time to the SB was only 1%. Across the 4 categories of birth/current residence in SB, there were large differences in demographic and stroke risk factors. Those born in the SB/not currently living in SB were primarily black, older on average, and had the highest prevalence of hypertensive medication use, diabetes, LVH, current smoking, and highest mean SBP compared to the other birth/current residence categories.

During a mean follow-up of 5.8 years (SD 1.9), 615 first-ever strokes occurred. Table 2 presents HRs and 95% CIs for stroke for the 4 categories of birth/current residence in or out of the SB. No significant differences were observed in the risk of stroke among the 4 groups but across all models, compared to those not born in SB/current residence outside the SB, risk of stroke was highest in those born and currently living in the SB, followed by those born in the SB and current residence outside the SB, followed by those not born in the SB but currently living in the SB.

Table 3 presents HRs and 95% CI for stroke associated with different exposure periods to living in the SB. After adjusting for age, race, and sex, the risk of stroke was significantly associated with 5 of the 8 exposure periods. The highest HR was for proportion of entire life in the SB (HR 1.23; 95% CI 1.04–1.45), followed by ages 0–12 (HR 1.22; 95% CI 1.04–1.42), ages 13–18 (HR 1.22; 95% CI 1.05–1.43), ages 19–30 (HR 1.19; 95% CI 1.01–1.40), and the last 20 years (HR 1.19; 95% CI 1.02–1.38). After additional adjustment for SES factors, the association was attenuated for all categories of SB exposure but remained significant for proportion of entire life in SB, first 12 years, ages 13–18, and last 20 years. After further adjustment for risk factors, the association was attenuated further with only the age period 13–18 years, remaining significantly associated with increased risk of stroke (HR 1.17; 95% CI 1.00–1.38). Pairwise statistical comparisons of effect estimates indicated that although some time periods were associated with increased risk of stroke, no 2 differed statistically from each other (all $p > 0.05$), and thus no single time period conferred higher risk than any other.

In race-stratified analysis (table 4), after adjustment for age and sex, there was a trend for higher relative stroke risk associated with SB residence among black than white subjects across all exposure periods; however, none reached statistical significance (p $\text{values}_{\text{interaction}} > 0.1$).

DISCUSSION Our study shows that the age period of living in the SB and length of time lived in the SB are associated with increased risk of incident stroke. After adjustment for demographic factors, and further adjustment for SES and stroke risk factors, living in the SB during the adolescence period (ages 13–18) emerged as the most important period of vulnerability. These findings support the theory that childhood life circumstances

Table 2 Association between incident stroke and birthplace and current residence in Stroke Belt

	Demographic model,[a] HR (95% CI)	Socioeconomic model,[b] HR (95% CI)	Framingham model,[c] HR (95% CI)
Born in SB and current residence in SB (n = 10,626)	1.17 (0.99–1.39)	1.15 (0.96–1.36)	1.11 (0.93–1.32)
Born in SB and current residence outside SB (n = 2,109)	1.04 (0.78–1.37)	1.02 (0.77–1.36)	1.03 (0.77–1.38)
Not born in SB but current residence in SB (n = 3,294)	1.01 (0.78–1.32)	1.01 (0.78–1.31)	0.95 (0.75–1.24)
Not born in SB and current residence outside the SB (n = 8,515)	Reference	Reference	Reference

Abbreviations: CI = confidence interval; HR = hazard ratio; SB = Stroke Belt.
[a] Age, race, and sex.
[b] Demographic model plus education and household income.
[c] Socioeconomic model plus Framingham stroke risk score variables: use of hypertensive medications, systolic blood pressure, history of heart disease, diabetes, left ventricular hypertrophy, atrial fibrillation, and current smoking.

associated with living in the SB more than later life exposures are associated with predisposition to diseases and risk factors later in life, both for those who continue to live in the SB as well as those who relocate to non-SB regions.

These results add to previous work relating SB birth and adult residence to stroke mortality: increased stroke mortality was associated independently with both being born in the SB and residence in the SB at time of death, with the highest stroke mortality in those who lived in the SB at birth and death.[14] Our results extend these findings to stroke incidence, and address possible causative pathways by providing adjustment for individual SES and stroke risk factors. With finer categorization of SB exposure, we found significantly increased stroke risk, supporting the hypothesis that the most important geographic characteristic is place of residence in adolescence. In addition, our findings confirm other work that examined self- or proxy-reported incident stroke and found that SB residence during childhood conveyed excess stroke risk regardless of adult residence.[6]

Over all categories of SB exposure, the increased stroke risk was present for both black and white subjects but the relative impact of living in the SB on stroke risk may be greater for black than for white subjects. We have previously shown the magnitude of increased stroke mortality was greater for black than white subjects.[25] In addition, previous research suggests racial disparities in stroke mortality may be due, in part, to black subjects living in regions with higher stroke mortality.[2,26] A study using data on birthplace reported that black residents from New York who were born in the South had higher cardiovascular mortality than those born in the Northeast.[13] Additionally, among deaths in South Carolina (a SB state), stroke mortality was highest among those born in the state, lower for those born in other southeastern states, and lowest for those born out of the Southeast; the protective effect of birthplace outside the Southeast was greater for black than white subjects.[12] Our results are consistent with these reports, with the highest stroke risk for those born and currently living in SB, followed by born in SB/current residence outside

Table 3 Association between proportion of life in the Stroke Belt and incident stroke

	Demographic model,[a] HR (95% CI)	Socioeconomic model,[b] HR (95% CI)	Framingham model,[c] HR (95% CI)
Proportion of entire life in SB	1.23 (1.04–1.45)	1.20 (1.01–1.42)	1.15 (0.97–1.37)
Partial life course exposure to SB			
Born in SB	1.15 (0.99–1.33)	1.12 (0.96–1.31)	1.11 (0.95–1.30)
Proportion of first 12 years	1.22 (1.04–1.42)	1.19 (1.02–1.40)	1.16 (0.99–1.37)
Proportion of ages 13–18	1.22 (1.05–1.43)	1.20 (1.03–1.40)	1.17 (1.00–1.37)
Proportion of ages 19–30	1.19 (1.01–1.40)	1.16 (0.99–1.37)	1.13 (0.96–1.34)
Proportion of ages 31–45	1.16 (0.99–1.35)	1.13 (0.97–1.32)	1.09 (0.93–1.28)
Proportion of last 20 years	1.19 (1.02–1.38)	1.17 (1.00–1.36)	1.12 (0.96–1.31)
Current residence in the SB	1.13 (0.98–1.32)	1.12 (0.96–1.30)	1.08 (0.92–1.26)

Abbreviations: CI = confidence interval; HR = hazard ratio; SB = Stroke Belt.
[a] Age, race, and sex.
[b] Demographic model plus education and household income.
[c] Socioeconomic model plus Framingham stroke risk score variables: use of hypertensive medications, systolic blood pressure, history of heart disease, diabetes, left ventricular hypertrophy, atrial fibrillation, and current smoking.

Table 4 Race-stratified association between proportion of different periods of life in the Stroke Belt and incident stroke, age/sex adjusted[a]

	Black HR (95% CI)	White HR (95% CI)
Proportion of entire life in SB	1.35 (1.04–1.74)	1.15 (0.93–1.42)
Partial life course exposure to SB		
Born in SB	1.26 (0.98–1.61)	1.08 (0.89–1.31)
Proportion of first 12 years	1.32 (1.03–1.69)	1.16 (0.95–1.41)
Proportion of ages 13–18	1.33 (1.04–1.68)	1.15 (0.95–1.40)
Proportion of ages 19–30	1.25 (0.98–1.60)	1.14 (0.92–1.40)
Proportion of ages 31–45	1.23 (0.97–1.55)	1.10 (0.90–1.35)
Proportion of last 20 years	1.28 (1.02–1.61)	1.12 (0.91–1.36)
Current residence in the SB	1.26 (1.00–1.57)	1.05 (0.86–1.28)
Born and current residence		
Born in SB and current residence in SB	1.34 (1.02–1.77)	1.07 (0.86–1.33)
Born in SB and current residence outside SB	1.11 (0.78–1.56)	1.09 (0.57–2.10)
Not born in SB but current residence in SB	1.02 (0.54–1.92)	0.99 (0.74–1.31)
Not born in SB and current residence outside the SB	Reference	Reference

Abbreviations: CI = confidence interval; HR = hazard ratio; SB = Stroke Belt.
[a] All interactions between race and exposure to the Stroke Belt were nonsignificant ($p > 0.10$).

SB, and lowest for those not born in SB but currently living there. Additionally, in race-stratified analyses, for all exposure periods, the risk of stroke associated with SB exposure was greater for black than white subjects.

Place of residence during childhood may contribute to the development of stroke risk through built environment, quality of education, access to care, socioeconomic conditions, exposure to stressors such as racial discrimination, and social norms influencing dietary patterns and other health behaviors and lifestyle choices. Southern states within the SB have been reported to have some of the poorest childhood health circumstances, including high rates of low birthweight, high infant, child, and teen mortality, and high teen birth rates.[27] In addition, areas of the Southeast have been shown to have among the lowest levels of healthy behaviors such as regular physical activity and the highest prevalence of cardiovascular risk factors such as hypertension and obesity.[28–31] These studies, though, are based on the current residence of respondents. Few US cohorts follow individuals from childhood through adulthood, so there is limited evidence on the contribution of childhood health behaviors to regional disparities in adult diseases. Cross-sectional data from REGARDS demonstrated that although birthplace and current residence in the SB were independently associated with prevalence of hypertension, residence in the SB during adolescence and early adulthood were significantly more predictive.[19] Ongoing research using REGARDS will link neighborhood and childhood/family characteristics with residential history for consideration of potential factors that may contribute to lifetime risk of stroke.

Adolescence and early adulthood are malleable periods of social and biological development during which individuals are more exposed to external influences and gain knowledge, resources, and courage to challenge or reaffirm their childhood habits and lifestyle. Many social and behavioral risk factors are set in place in adolescence. One example is smoking initiation, which is highest during adolescence.[32] Many adolescents make decisions about education, marriage, and work that will impact their social context for the rest of their lives. In a review of data on the effects of parental attitudes and styles on a child's nutritional behavior, strong correlations were found between parent and child on food intake, eating motivations, and body dissatisfaction and satisfaction, suggesting that parental modeling may be the best method for reinforcing healthy eating and potentially other healthy habits.[33,34] While there are many potential pathways in which adolescent behaviors contribute to the development of stroke risk factors, we cannot separate out lifestyle factors from environmental factors associated with living in the SB.

The finding that greater exposure to SB in the last 20 years was significantly associated with stroke risk in the SES demographic adjusted model but that current residence in SB was not, and that the association is no longer significant after adjustments for stroke risk factors, suggests that factors associated with living in the SB have a cumulative effect to increase stroke risk and may be in the causal pathway of the increased risk in the SB. However, these measures of SB exposure are highly correlated, where those with high childhood exposure to the SB are also more likely to have high adult exposure.

REGARDS is one of few cohort studies in the United States with residential history data starting at birth. Other strengths include a large national population sample of black and white subjects, with oversampling of current residents of the SB, measured prestroke risk factors, and physician-adjudicated incident strokes. There are also some limitations. Those who agreed to participate in REGARDS may not be representative of the general population, potentially reducing generalizability of our results. We do not have data on childhood SES status or changes in SES status over the participant's lifetime that likely impact development of risk factors as well as migration patterns. The information on stroke risk factors is from recent exposure periods during adulthood and we do not have data on earlier exposure periods. Research is underway to examine other ways to compose the SB exposure variable (e.g., none vs ever), and also to specifically examine exposure to the stroke buckle region, an area of even greater stroke mortality than the overall SB.[16]

Our data suggest that living in the SB during adolescence may contribute to the higher stroke mortality in the SB, and the harmful effects associated with living in the SB may be greater for black than white subjects. Improvement in childhood health circumstances should be considered as part of long-term health improvement strategies.

AUTHOR CONTRIBUTIONS

Dr. V. Howard and Dr. McClure had access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Dr. V. Howard, Dr. G. Howard, Dr. Lackland. Acquisition of data: Dr. V. Howard, Dr. McClure, Dr. G. Howard, F. Peace. Analysis and interpretation of data: Dr. V. Howard, Dr. McClure, Dr. Glymour, Dr. Cunningham, Dr. G. Howard. Drafting of the manuscript: Dr. V. Howard. Critical revision of the manuscript for important intellectual content: Dr. V. Howard, Dr. McClure, Dr. Glymour, Dr. Cunningham, Dr. Kleindorfer, Dr. Crowe, Dr. Wadley, F. Peace, Dr. G. Howard, Dr. Lackland. Obtained funding: Dr. V. Howard, Dr. Glymour, Dr. Cunningham, Dr. Crowe, Dr. Wadley, Dr. G. Howard. Administrative, technical, and material support: Dr. V. Howard, F. Peace, Dr. G. Howard. Study supervision and coordination: Dr. V. Howard, Dr. G. Howard.

STUDY FUNDING

Supported by NIH NS041588 and AG039588. The REGARDS 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. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke or the NIH. Representatives of the funding agency have been involved in the review of the manuscript but not directly involved in the collection, management, analysis, or interpretation of the data. V.J.H., M.M.G., S.A.C., M.C., and V.G.W. received additional support from an investigator-initiated R01 AG039588 from the National Institute of Aging. The authors thank the other investigators, the staff, and the participants of the REGARDS study for their contributions. A full list of participating REGARDS investigators and institutions can be found at http://www.regardsstudy.org.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received August 25, 2012. Accepted in final form December 19, 2012.

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