The Reasons for Geographic and Racial Differences in Stroke Study: Objectives and Design

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Key Words
Cerebrovascular disorders, epidemiology · Cohort studies · Epidemiologic methods · African-Americans · Risk factors · Geography · Southeastern United States · Prospective studies

Abstract
The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study is a national, population-based, longitudinal study of 30,000 African-American and white adults aged ≥ 45 years. The objective is to determine the causes for the excess stroke mortality in the Southeastern US and among African-Americans. Participants are randomly sampled with recruitment by mail then telephone, where data on stroke risk factors, sociodemographic, lifestyle, and psychosocial characteristics are collected. Written informed consent, physical and physiological measures, and fasting samples are collected during a subsequent in-home visit. Participants are followed via telephone at 6-month intervals for identification of stroke events. The novel aspects of the REGARDS study allow for the creation of a national cohort to address geographic and ethnic differences in stroke.

The ‘Stroke Belt’ was first identified in 1965 as a region of high stroke mortality in the Southeastern US [1], and it is frequently defined as including 8 southern states: North Carolina, South Carolina, Georgia, Tennessee, Mississippi, Alabama, Louisiana, and Arkansas. Excess stroke mortality rates in this region have been documented since at least 1940 [2] and despite minor geographic shifts [3], they still persist [4, 5]. Within the Stroke Belt, a ‘Buckle’ region along the coastal plain of North Carolina, South Carolina, and Georgia has been identified with even a higher stroke mortality rate than the remainder of the Stroke Belt (fig. 1) [6].

Two recent reviews identified at least 10 published hypotheses of the causes of the Stroke Belt [5, 7]. These hypotheses include an array of potential causes as divergent as differences in socioeconomic status, quality of health care, lifestyle choices (including diet), and differ-
ences in major cardiovascular risk factors, including hyper-

tension [7]. Despite the potential public health impact of the Stroke Belt, few data are available addressing these hypotheses, and it is not even known whether regional differences in stroke incidence contribute to this excess stroke mortality.

In addition, overall stroke mortality rates among African-Americans are about 50% higher than whites with the largest disparity at younger ages [8, 9]. Like the excess stroke mortality in the Southeast, little is known about the causes underlying the excess stroke mortality in blacks.

Most large population-based epidemiological studies have been conducted in predominantly white communities (e.g. Framingham, Mass., and Rochester, Minn., USA) [10, 11]. As a result, little is known about stroke incidence among African-Americans. The exception to this is the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS), which is estimating stroke incidence in a racially mixed community [9]. Early results from that study suggest a substantial excess incidence of stroke in African-Americans, primarily in the population below age 65, with no excess seen in the oldest age group [9]. While that study has provided important insights into racial differences in stroke incidence, it is limited to a single geographic region.

There are even fewer data available addressing racial differences in the role of stroke risk factors. The exception is the National Health and Nutrition Examination Survey (NHANES), and while it is not optimally designed to describe geographic variations in stroke risk factors, it has provided key national data on prevalence of risk factors by ethnic group [12]. NHANES focuses on a broad spectrum of diseases, and therefore does not describe all stroke risk factors.

Based on very limited data, the excess stroke mortality in African-Americans may be attributed in part to a higher incidence rate. Gillum, on behalf of the Centers for Disease Control, recently proposed recommendations for population-based research on stroke mortality in African-Americans [13]. Among these recommendations is a call for the use of various study designs to assess the

![Fig. 1. Map of US counties showing regions in the REGARDS study.](image-url)
role of racial differences in stroke subtype distribution, incidence, case fatality, recurrence, competing mortality, utilization of therapeutic stroke care, population prevalence of stroke and heart disease, hypertension control, and diabetes prevalence on the excess mortality in blacks, the slowdown in the decline of mortality rates, and the geographic variation in stroke [13]. This recommendation addresses almost all aspects of the epidemiology of racial/ethnic differences in stroke.

The REasons for Geographic And Racial Differences in Stroke (REGARDS) study was designed to elucidate factors underlying the excess stroke mortality in the Southeastern US and among African-Americans. Here, we describe the REGARDS study design.

**Objectives of REGARDS**

The primary aims of REGARDS are associated with geographic and racial/ethnic (African-American vs. white) differences in stroke. The primary aims are:

1. To provide national data on stroke incidence and case fatality and assess geographic variations and racial differences in these measures.
2. To provide national data on prevalence and levels of stroke risk factors and assess geographic and racial variation in the prevalence of these risk factors.
3. To assess the degree to which geographic and racial variations in stroke incidence, case fatality and mortality are attributable to variations in risk factor prevalence.
4. To assess geographic and racial variations in the magnitude of the impact of prevalent stroke risk factors.
5. To assess the impact of migration on stroke incidence, case fatality and mortality.
6. To create a blood, urine and DNA repository as a resource for future studies.

**Design and Methods**

The organization of REGARDS comprises an Operations Center and the Survey Research Unit (SRU) at the University of Alabama at Birmingham, a Central Laboratory at the University of Vermont, an Electrocardiogram (ECG) Reading Center at Wake Forest University, an in-home exam component provided by Examination Management Services, Inc. (EMSI), and a medical monitoring and stroke adjudication center at Alabama Neurological Institute, Inc. An Executive Committee comprising the principal investigator of each study center and a National Institute of Neurological Disorders and Stroke representative assists the principal investigator at the University of Alabama at Birmingham in the scientific leadership of the study. Study methods were reviewed and approved by all involved institutional review boards, as well as an external observational study monitoring board appointed by the funding agency.

**Sampling, Recruitment, and Initial Telephone Interview**

The REGARDS sample is selected from a commercially available nationwide list purchased through Genesys Inc., stratified to reflect the specific age-race-sex-geographic strata described below. Sample listings are purchased in batches of 50,000 households to ensure the most current telephone numbers and addresses. Criteria for inclusion in the sample include having a name, telephone number and address in the Genesys database. The recruitment goal of 30,000 participants includes 30% from the Stroke Belt, 20% from the Stroke Buckle, and the remainder from elsewhere in the continental U.S. Within each region, approximately one half will be white and one half African-American, and within each region-race stratum, approximately one half will be male and one half female.

A letter and study brochure are sent to each potential participant approximately 2 weeks prior to attempting telephone contact. Initially, only the individual listed in the database was considered a potential participant. After recruitment of approximately ¼ of the sample, because of concerns that non-heads-of-household could be underrepresented by the commercially available list, a household enumeration approach and selection of a ‘random’ household member was implemented. Trained interviewers make up to 15 contact attempts during day, evening, weekday and weekend calling shifts. Upon reaching a household resident, the household is enumerated and one resident aged ≥45 is randomly selected and screened for eligibility. Exclusion criteria include race other than African-American or white, active treatment for cancer, medical conditions that would prevent long-term participation, cognitive impairment judged by the telephone interviewer, residence in or inclusion on a waiting list for a nursing home, or inability to communicate in English. Potential participants who respond ‘don’t know’ to questions about medical conditions are considered eligible.

Once eligibility is established, respondents are asked for their verbal informed consent. Prior to agreeing to participate in the study, the participant is told that he/she will be contacted to arrange a convenient time and place (usually in their home) to collect physical measurements, blood and urine samples. Following verbal consent, the medical history, including risk factor evaluation, is collected by computer-assisted telephone interviewing (CATI). CATI (rather than in-home interview) is used to collect these data in order to provide a higher level of quality control and standardization by using trained, certified and monitored staff of the SRU. It also allows for the assessment of differences in the characteristics of participants completing and not completing the in-home exam.

**In-Home Exam**

Following the telephone interview, the participant’s contact information is transmitted to EMSI for scheduling of the in-home visit. During scheduling, the participant is reminded to fast overnight for 10–12 h before the visit and is asked to have medications available for recording at the time of the visit. The visit takes place on Monday–Thursday mornings to permit fasting status and allow time for specimen processing and shipping for receipt the following day at the central laboratory. EMSI technicians who are trained on methods for the REGARDS protocol complete the in-home vis-
its and ship samples to the central laboratory. If the participant changes his/her mind or for some other reason the in-home visit is not completed, he/she is then classified as a partial participant.

At the in-home visit, trained EMSI personnel review and obtain written informed consent from the participant. Physical measurements, a resting ECG, medication inventory, phlebotomy and urine collection are performed using standardized methods. If the participant is willing to provide it, the social security number is obtained for tracking purposes. Self-administered questionnaires are left with the participant to gather information on additional demographic and risk factor characteristics. These questionnaires are completed by the participant after the home visit and are returned to the Operations Center by self-addressed prepaid envelopes. Any problems (e.g. missing or incomplete data) are resolved via follow-up telephone contact. Participants are mailed a thank-you letter and a $30 check approximately 6–8 weeks following the in-home visit.

Sample Size and Power

The sample size of REGARDS was calculated to provide a sufficient number of stroke events to detect associations with risk factors with relatively small differences in risk (i.e. small hazard ratios). When REGARDS was initially being planned, most of the information on stroke incidence was from predominately white and northern communities, specifically Framingham, Mass., and Rochester, Minn., USA [14, 15]. Subsequently, the GCNKSS provided valuable information on the anticipated stroke incidence rates in a community with adequate representation of blacks and whites [16]. These data were used to calculate the anticipated number of events per 1,000 person-years exposure for each race-sex strata (table 1). Specifically, we anticipate 55.0 events per year for black males, 52.3 events per year for black females, 36.1 events per year for white males, and 34.6 events per year for white females. This provides an estimated stroke event rate of 10.8 events per year from this stratum.

Table 1. Expected rate of stroke events in REGARDS per 1,000 person-years exposure

<table>
<thead>
<tr>
<th>Age group</th>
<th>Black males</th>
<th>Black females</th>
<th>White males</th>
<th>White females</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–54</td>
<td>307.3</td>
<td>308.4</td>
<td>158.6</td>
<td>85.3</td>
</tr>
<tr>
<td>55–64</td>
<td>565.7</td>
<td>498.1</td>
<td>285.0</td>
<td>197.9</td>
</tr>
<tr>
<td>65–74</td>
<td>1,169.6</td>
<td>995.7</td>
<td>728.9</td>
<td>476.7</td>
</tr>
<tr>
<td>75–84</td>
<td>2,388.8</td>
<td>1,520.7</td>
<td>1,259.9</td>
<td>1,196.0</td>
</tr>
<tr>
<td>85+</td>
<td>2,599.1</td>
<td>2,285.6</td>
<td>1,902.6</td>
<td>1,748.5</td>
</tr>
</tbody>
</table>

Table 2. Detectable hazard ratio with 80 and 90% power, by prevalence of a risk factor (for 534 events)

<table>
<thead>
<tr>
<th>Power</th>
<th>Prevalence of risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>80%</td>
<td>1.74</td>
</tr>
<tr>
<td>90%</td>
<td>1.90</td>
</tr>
</tbody>
</table>
The EMSI examiner records prescription and nonprescription medications taken within the previous 2 weeks, and leaves the self-administered questionnaires with the participant. These include a ‘Places You Have Lived’ questionnaire, the Block 98 Food Frequency Questionnaire [28], a family history questionnaire for stroke, heart attack, and death in parents and siblings, and a contact information questionnaire. Tracking information, including contact information for two relatives or friends not living with the participant, is requested. In the residential history questionnaire, the participant records the city and state of birth, and all other cities and states in which he/she has lived (including dates) up to the present residence.

The length of the in-home visit is 45–60 min. All appropriate paperwork is completed, verified and reviewed with the participant to ensure accuracy. The EMSI staff reminds the participant to complete and mail the self-administered questionnaires and reiterates that he or she will be contacted by telephone every 6 months. A card including his/her height, weight, blood pressure and pulse, and a brochure on stroke warning signs are given to the participant during the in-home examination. For questions, the participant is encouraged to contact the Operations Center through a toll-free number.

Data Handling and Processing

At the local EMSI office, the in-home visit status is updated in a schedule tracking system. Blood samples are centrifuged at approximately 20,000 g at room temperature and the serum, plasma, cell layer, and urine are placed in transfer vials and stored in a refrigerator until pick-up by a courier on the same day. Samples are shipped overnight with ice packs (PolarPack® Tough Pack, Thermosafe Brands, New Brighton, Pa., USA) along with the signed informed consent, bar-code labeled ECG and other paperwork to the Central Laboratory. If samples are not received within 24 h of collection, the participant may be contacted for a re-draw appointment.

Upon receipt, technicians at the Central Laboratory unpack and examine the samples, log the contents, and re-centrifuge the serum and plasma samples at 60,000 g and 4°C. Samples are either analyzed or transferred to storage cryovials for the repository. Study paperwork is forwarded to the Operations Center and ECGs to the ECG Reading Center. Upon receipt at the ECG Reading Center, the ECGs are immediately read for abnormalities. All ECGs have critical wave form durations measured and the ECGs are coded using the standardized Minnesota Code [29, 30].

Notification of and Referral for Study Findings

One of the benefits to study participants is the provision of screening for stroke risk factors at no cost to them. Participant feedback is based on the urgency for medical attention, using guidelines from the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [31], the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [32], and the American Diabetes Association criteria for diabetes mellitus [33]. Participants are notified if any of the medical problems listed in table 4 are detected. The ‘critical’ values trigger immediate notification in the home or by telephone contact within 2 days of receipt of results. Once all data are verified, a report is mailed to the participant within 6–8 weeks, summarizing laboratory results (lipid panel, glucose, and creatinine) and whether the ECG was abnormal. For ‘alert’ values, the participant is advised to seek medical attention in the near future. For ‘notification’ values, the particip-

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**Table 3. Components of the REGARDS telephone and in-home baseline examination**

<table>
<thead>
<tr>
<th>Component</th>
<th>Telephone interview</th>
<th>In-home exam</th>
<th>Self-administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Personal history, demographic data,</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>socioeconomic status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke-free status</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical activity</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Depression</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cognitive screening</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Perceived health/quality of life</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Social support</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Social network</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Potential caregiver</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Laboratory assays(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Height, weight, waist circumference</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood pressure, pulse</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Electrocardiography(^b)</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medications in the past 2 weeks</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Residential history</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dietary intake</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Family history</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

\(^a\) Lipid profile, glucose, creatinine, C-reactive protein.

\(^b\) Initially, the electrocardiography was a modified 7-lead; it was changed to a 12-lead in May 2004.
Participant Follow-Up for Stroke Events

The study conducts active surveillance of cohort members to ascertain, validate and classify fatal and non-fatal stroke outcomes. Participants are contacted by telephone at 6-month intervals over the follow-up period extending up to 4 years. Data are collected on suspected events that require hospitalization, as well as on physician evaluations for stroke-like symptoms detected using the Questionnaire for Verifying Stroke-Free Status [23]. If the participant is unable to respond to follow-up telephone calls for medical reasons, a proxy respondent identified by the participant at baseline will be interviewed.

If a participant is hospitalized or sees a physician for stroke-like symptoms, contact information for the hospital and/or physician is obtained from the participant, and pertinent in- and outpatient medical records are sought. Medical records retrieval is initiated by having the participant sign a permission form for release of records. If a death is reported, the death certificate and associated hospital or physician records are collected, including medical records for the 28-day period preceding death. If death occurred within a month following a procedure, information on that procedure is obtained from the participant, and pertinent in- and outpatient medical records are sought. Medical records retrieval is initiated by having the participant sign a permission form for release of records. If a death is reported, the death certificate and associated hospital or physician records are collected, including medical records for the 28-day period preceding death. 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Personnel Training and Quality Control

Approximately 100 telephone interviewers, approximately half of whom are African-American, are carefully trained and closely monitored for sensitivity to the attitudes, abilities, and limitations of study participants. Training of telephone interviewers and the more than 6,500 EMSI examiners emphasizes the importance of participant privacy and the confidentiality of personal information. An interviewer’s performance is continuously monitored by SRU supervisors, and group meetings are held periodically with the REGARDS Operations Center personnel to discuss frequently asked questions and to resolve unusual circumstances. EMSI examiners are trained at their local offices by centrally-trained supervisors. Training includes a web-based REGARDS-specific program that is also available for continuing reference and retraining if needed. Feedback is provided at periodic intervals and when needed, based on review of data.

Data Management

A single data management system integrates data from all sources. Interview information collected during the telephone con-

Table 4. Thresholds for risk factor reporting to participants

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Critical valuea</th>
<th>Alert valueb</th>
<th>Notification valeyc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>&gt;180</td>
<td>&gt;140</td>
<td>none</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>&gt;110</td>
<td>&gt;90</td>
<td>none</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>none</td>
<td>&gt;200</td>
<td>none</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>none</td>
<td>&gt;130</td>
<td>none</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>none</td>
<td>&lt;40</td>
<td>none</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>&gt;1,000</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>&gt;200</td>
<td>&gt;126</td>
<td>&gt;110</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>&gt;2.5</td>
<td>&gt;1.5</td>
<td>left bundle branch block, atrial fibrillation, minor abnormalities</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>Wolf-Parkinson white, acute myocardial infarction, acute pericarditis, other acute finding</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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a Require notification by telephone with instructions to immediately seek care.
b Require notification by mail with instructions to promptly seek care.
c Require notification by mail with instructions to discuss results with a health care professional at next scheduled visit.
tact is entered as part of the CATI system. Data from the in-home and self-administered questionnaires are scanned and processed by an in-house system similar to the Teleform® system. Data from the Central Laboratory, the ECG Reading Center and EMSI are transmitted daily by internet.

Discussion

Geographic and racial disparities in stroke mortality rates are well documented, but their causes remain a mystery. Current sources of data, while providing useful descriptive information, cannot adequately address underlying reasons for these disparities. For example, national surveys, such as NHANES, record multiple diseases and health conditions and do not address the breadth of stroke risk factors [12]. Traditional cardiovascular epidemiologic cohort studies are clinic based, so they are not designed to explore geographic variations in disease [10, 11, 18–20]. In addition, several of these studies have confounded geography and race, as in the Atherosclerosis Risk in Communities study, where the majority of African-Americans are from a single site [18]. Retrospective studies, such as the Northern Manhattan Stroke Study, are addressing risk factors contributing to racial differences in stroke using a case-control design. Retrospective assessment of risk factors complicates interpretation of the results when risk factors change after a stroke event. The Northern Manhattan Stroke Study also has a community cohort of approximately 3,000 participants, and the small number of anticipated stroke events limits statistical power [40]. Surveillance studies, such as the GCNKSS, also identify stroke patients after the event [9].

Due to the limitations of existing studies, a national cohort study focusing specifically on stroke is needed to address important questions of racial and geographic disparities. A principal barrier to such a study has been the large sample size needed to generate a sufficiently large number of events for reliable estimation of associations with risk factors.

REGARDS uses an innovative study design to meet its objectives. Though national in scope, REGARDS is managed, and participants are recruited and largely evaluated through a single site. The absence of clinical centers allows recruitment of a large cohort in a cost-effective manner. The need to assess undiagnosed risk factors (such as hypertension, diabetes, and dyslipidemia), however, requires physical contact with participants. REGARDS has met this need by subcontracting with a national company with employees located in all regions of the nation who are trained and equipped to assess stroke risk factors. While the complexity and quality of data collected by these methods may not reach the level obtainable in clinic-based epidemiological studies, this approach permits efficient study of a true national sample.

Due to the novel design of REGARDS, prior experience in management of such a study is not available. Thus, for most elements of the study, significant pilot testing was carried out. These pilot studies were conducted to evaluate household enumeration of potentially eligible participants, assess the feasibility of including tests of cognitive function and develop and refine alternative methods for scheduling in-home visits.

There are several efforts currently underway to enrich the REGARDS data set. One is to provide for geocoding of participant residences. Because the participants are randomly chosen from across the nation, the value of linking community indices of socio-economic status from the Census Bureau, measures of water quality and content from the Environmental Protection Agency, measures of weather from the National Oceanic and Atmospheric Administration Weather Service, and other indices is substantial.

With the large sample size, it is anticipated that approximately 500 incident strokes will occur during follow-up. This will allow REGARDS to identify risk factors that may contribute to racial and geographic disparities in stroke incidence and mortality and to assess whether there are differences by race or geography in the impact of baseline risk factors.

In conclusion, Cooper’s 1993 ‘call to action’ to advance the understanding of the excess African-American stroke mortality stated that it was ‘urgent that renewed research and medical interventions be undertaken to address this crisis’ [41]. In a recent similar call by Gillum [13], many of the same issues persist. REGARDS is designed to provide the necessary data to better understand the sources of the racial and geographic disparities in stroke. Successful completion of the study should provide guidance for interventions to reduce this immense public health burden.

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