

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

Virginia J. Howard^a Mary Cushman^c LeaVonne Pulley^d Camilo R. Gomez^e
Rodney C. Go^a Ronald J. Prineas^f Andra Graham^g Claudia S. Moy^h
George Howard^b

Departments of ^aEpidemiology and ^bBiostatistics, University of Alabama at Birmingham, Birmingham, Ala., ^cDepartments of Medicine and Pathology, Laboratory for Clinical Biochemistry Research, University of Vermont, Burlington, Vt., ^dDepartment of Health Behavior, University of Arkansas Health Science University, Little Rock, Ark., ^eAlabama Neurological Institute, Birmingham, Ala., ^fDepartment of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, N.C., ^gExamination Management Services, Incorporated, Dallas, Tex., and ^hNational Institute of Neurological Disorders and Stroke, Rockville, Md., USA

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.

Copyright © 2005 S. Karger AG, Basel

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-

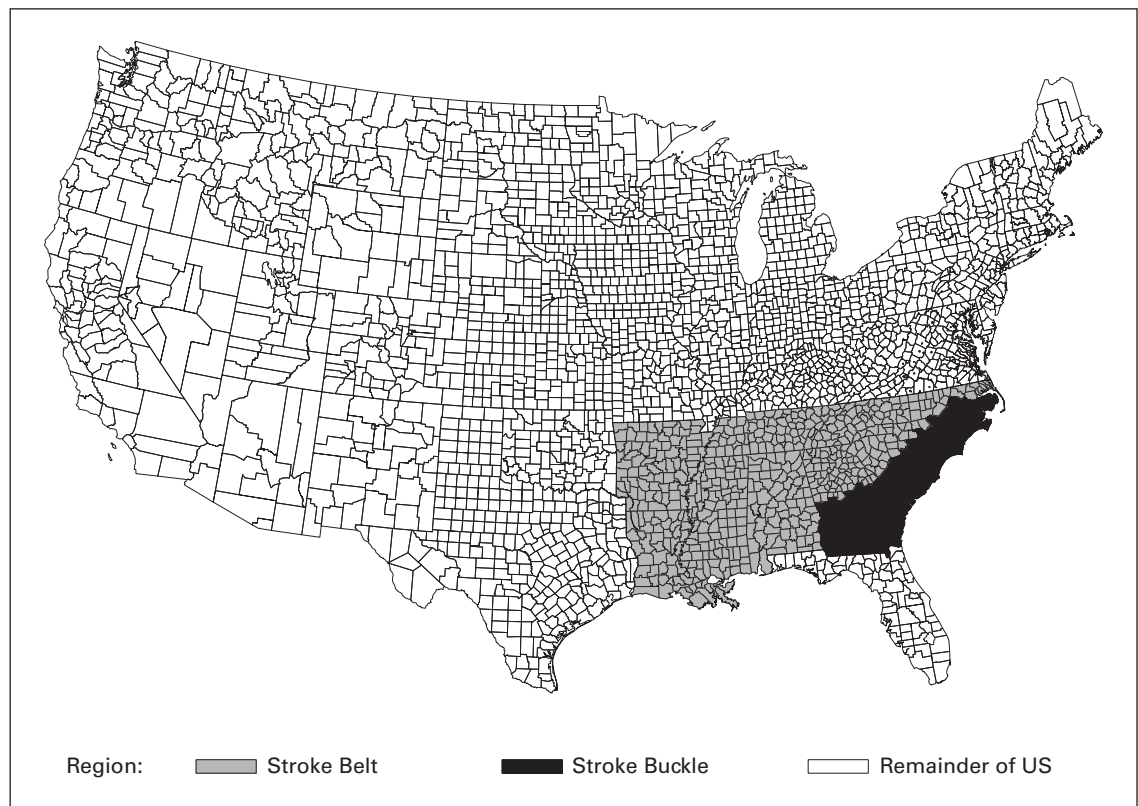


Fig. 1. Map of US counties showing regions in the REGARDS study.

ences in major cardiovascular risk factors, including hypertension [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

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 1/4 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 the use of 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-

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

Age group	Black males			Black females			White males			White females		
	population event rate ^a	percent of population ^b	expected annual events in REGARDS ^c	population event rate ^a	percent of population ^b	expected annual events in REGARDS ^c	population event rate ^a	percent of population ^b	expected annual events in REGARDS ^c	population event rate ^a	percent of population ^b	expected annual events in REGARDS ^c
45–54	307.3	47%	10.8	308.4	42%	9.7	158.6	40%	4.8	85.3	35%	2.2
55–64	565.7	26%	11.2	498.1	25%	9.3	285.0	26%	5.6	197.9	24%	3.5
65–74	1,169.6	17%	14.5	995.7	18%	13.5	728.9	19%	10.5	476.7	20%	7.0
75–84	2,388.8	8%	14.4	1,520.7	11%	12.4	1,259.9	12%	11.0	1,196.0	15%	13.7
85+	2,599.1	2%	4.1	2,285.6	4%	7.5	1,902.6	3%	4.2	1,748.5	6%	8.1
Events	55.0			52.3			36.1			34.6		

^a Number of events per 100,000 person-years [14].

^b For each race-sex strata, the percent of US population above age 45 within each age strata [ref. 42: table P12A for whites, table P12B for blacks].

^c For example, we expect one fourth of the 30,000 participants, or 7,500 participants, to be African-American men. In the general population, 47% are African-American men between 45 and 54 years of age; hence, we expect approximately 3,525 black male participants between the age of 45 and 54. From the GCNKSS, the stroke rate for this population is 307.3/100,000; hence, we anticipate 10.8 events per year from this stratum.

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 expected 178.1 stroke events annually, and with approximately 3 years follow-up, a total of 534.3 stroke events.

Using the approaches of Schoenfeld [17], the detectable hazard ratio can be calculated as a function of the prevalence of the predic-

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

Power	Prevalence of risk factor					
	5%	10%	20%	30%	40%	50%
80%	1.74	1.50	1.35	1.30	1.28	1.28
90%	1.90	1.59	1.42	1.36	1.33	1.32

tor risk factor (table 2). For common predictor factors with a prevalence of 30% or more (but less than 70%), a hazard ratio less than 1.30 can be detected with 80% power and a hazard ratio of 1.36 with 90% power. Even for 'rare' predictor factors with a prevalence of 5% (or a very common predictor with prevalence greater than 95%) a hazard ratio of 1.74 can be detected with 80% power and 1.90 with 90% power.

Data Collected

Components of the baseline evaluation are provided in table 3. The format and content of the medical history and risk factor questionnaire (collected by CATI) are similar to previous studies of cerebrovascular and cardiovascular risk factors [10, 18–20]. Variables include age, race, and sex of the participant, history of valvular heart disease, kidney disease, reproductive history (if female), aspirin use, cigarette smoking (including smoking status, pack-years exposure, and exposure to passive cigarette smoke), alcohol intake, physical activity level, general health (MOS Short Form-12) [21], access to care, insurance status, marital status, measures of socioeconomic status (education and income) and social network [22], psychosocial factors (social network, depressive symptoms, and stress), and history of cardiovascular procedures (endarterectomy, coronary artery bypass surgery, peripheral vascular surgery, and percutaneous transluminal coronary angioplasty).

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

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

^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.

ty), myocardial infarction or stroke. Previous stroke symptoms are assessed using the Questionnaire for Verifying Stroke-Free Status [23]. Depressive symptoms are assessed by the Center for Epidemiologic Studies Depression Scale [24] and Cohen's Perceived Stress Scale [25]. Cognitive function is assessed by the Six-Item Cognitive Screener [26]. The duration of the telephone interview is 30–45 min.

During the in-home visit, EMSI personnel take two blood pressure measurements utilizing a standard aneroid sphygmomanometer. Blood pressure quality control is monitored by central examination of digit preference, and retraining of technicians takes place if necessary. Height is obtained utilizing an 8-foot metal tape measure and a square, and weight (without shoes) is obtained using a standard 300-lb calibrated scale. Venipuncture is performed using standardized methods and a random urine sample is collected. Quality control of the samples is monitored as in other large cohort studies [27]. Samples are immediately placed in a cooler with ice packs for transport to the local EMSI field office. A 12-lead ECG is obtained using several electrocardiograph models available from EMSI. The ECGs are recorded at standard 25 mm/s speed and calibrated to 10 mm = 1 mV.

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 partici-

Table 4. Thresholds for risk factor reporting to participants

Risk factor	Critical value ^a	Alert value ^b	Notification value ^c
Systolic blood pressure, mm Hg	>180	>140	none
Diastolic blood pressure, mm Hg	>110	>90	none
Total cholesterol, mg/dl	none	>200	none
LDL cholesterol, mg/dl	none	>130	none
HDL cholesterol, mg/dl	none	<40	none
Triglycerides, mg/dl	>1,000	none	none
Glucose, mg/dl	>200	>126	>110
Creatinine, mg/dl	>2.5	>1.5	none
Electrocardiography	Wolf-Parkinson white, acute myocardial infarction, acute pericarditis, other acute finding	left bundle branch block, atrial fibrillation, other serious finding	minor abnormalities

^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.

participant is advised to review them with his/her physician at the next regular visit.

Participant Follow-Up for Stroke Events

The study conducts active surveillance of cohort members to ascertain, validate and classify fatal and nonfatal 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 collected. If medical records are unavailable or judged insufficient by the Events Committee, a physician questionnaire for decedents or an informant interview questionnaire will be completed using methods developed and used in other studies [34–36].

The protocol for event verification is based on methods developed for previous stroke clinical trials [36, 37] and observational studies [34, 35]. Information related to geographic region and race is masked and the documents are copied and sent to two members of the Events Committee. Committee members review the records independently using criteria for stroke and stroke subtypes similar to the GCNKSS and TOAST (Trial of ORG 10172 in Acute Stroke Treatment) [9, 38]. The adjudication process validates stroke occurrence, and also classifies events by stroke ‘subtype’ and severity

(using the National Institutes of Health Stroke Scale) [39]. An incident stroke is defined as: ‘rapid onset of a persistent neurologic deficit attributable to an obstruction or rupture of the arterial system (including stroke occurring during a procedure such as angiography or surgery); deficit is not known to be secondary to brain trauma, tumor, infection, or other non-ischemic cause; deficit must last more than 24 h, unless death supervenes or there is a demonstrable lesion compatible with acute stroke on computed tomography or magnetic resonance imaging’. For every potential event reviewed, each adjudicator completes an Events Form and submits it to the Operations Office. No further action is needed if the two reviewers agree on the occurrence of stroke and stroke subtype. In cases of disagreement, a third adjudicator reviews the potential event. For all deaths, the underlying and contributing causes will also be classified by the Events Committee.

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-

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 na-

tional 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.

Acknowledgements

This research project is supported by a cooperative agreement U01 NS041588 from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Department of Health and Human Services.

REGARDS Investigators and Staff

University of Alabama at Birmingham: George Howard (principal investigator), Charles Alcorn, Tysie E. Baker, Ruth Brinker, Ronald A. Cantrell, Mickey Doubleman, H. Russell Foushee, Rodney Go, Marie Gray, Michael Harbin, Shannon Houser, Virginia J. Howard, Patricia A. Johnson, Martha Kellum, Doug Kennedy, Kim McCain, Leslie A. McClure, Richard Mailhot, Margaret S. Stewart, Ella M. Temple, Lindsay J. Tillery, Virginia G. Wadley, Libby Wagner, Ruth Wellborn, Andrew O. Westfall, Corey Wiggins, Tony Wilson.

University of Vermont, Central Laboratory: Mary Cushman (principal investigator), Rebekah Boyle, Elaine S. Cornell, Andrew Bessy, Diane Wells, Nicole Gagne, Lawrence Houston, Lynsey Provost.

Wake Forest University School of Medicine, ECG Reading Center: Ronald J. Prineas (principal investigator), Lisa Billings,

Charles N. Campbell, Zachary Hollis, Yabing Li, Zhu-Ming Zhang.

Alabama Neurological Institute, Medical Monitoring and Events Adjudication: Camilo Gomez (principal investigator), Nancy Lemons, Sean Orr, David Rhodes.

Examination Management Services, Inc., In-Home Exam Component: Andra Graham (project manager), Regina Dickerson, Kathy Gainer, Susan Gilmartin.

Consultants: LeaVonne Pulley, University of Arkansas for Medical Sciences; David Goff, Wake Forest University School of Medicine; Meir Stampfer, Harvard School of Public Health.

National Institute of Neurological Disorders and Stroke, Project Office: Claudia S. Moy (program officer), John R. Marler.

References

- 1 Borhani NO: Changes and geographic distribution of mortality from cerebrovascular disease. *Am J Public Health* 1965;55:673-681.
- 2 Lanska DJ: Geographic distribution of stroke mortality in the United States: 1939-1941 to 1979-1981. *Neurology* 1993;43:1839-1851.
- 3 Casper ML, Wing S, Anda RF, Knowles M, Pollard RA: The shifting stroke belt. Changes in the geographic pattern of stroke mortality in the United States, 1962 to 1988. *Stroke* 1995;26:755-760.
- 4 Howard G, Evans GW, Pearce K, Howard VJ, Bell RA, Mayer EJ, Burke GL: Is the stroke belt disappearing? An analysis of racial, temporal, and age effects. *Stroke* 1995;26:1153-1158.
- 5 Perry HM, Roccella EJ: Conference Report on Stroke Mortality in the Southeastern United States. *Hypertension* 1998;31:1206-1215.
- 6 Howard G, Anderson R, Sorlie P, Andrews V, Russell G, Howard VJ: Evaluation of social status as a contributing factor to the stroke belt region of the United States. *Stroke* 1997;28:936-940.
- 7 Howard G: Why do we have a stroke belt in the southeastern United States? A review of unlikely and uninvestigated potential causes. *Am J Med Sci* 1999;317:160-167.
- 8 Howard G, Anderson R, Sorlie P, Andrews V, Backlund E, Burke GL: Ethnic differences in stroke mortality between non-Hispanic whites, Hispanic whites, and blacks. *The National Longitudinal Mortality Study. Stroke* 1994;25:2120-2125.
- 9 Broderick J, Brott T, Kothari R, Miller R, Khoury J, Pancioli A, Gebel J, Mills D, Minneci L, Shukla R: The Greater Cincinnati/Northern Kentucky Stroke Study: Preliminary first-ever and total incidence rates of stroke among blacks. *Stroke* 1998;29:415-421.
- 10 Kannel WB: The Framingham Study: Its 50-year legacy and future promise. *J Atheroscler Thromb* 2000;6:60-66.
- 11 Melton LJ III: History of the Rochester Epidemiology Project. *Mayo Clin Proc* 1996;71:266-274.
- 12 Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-1994. Series 1: Programs and collection procedures. *Vital Health Stat* 1994;32:1-407.
- 13 Gillum RF: Stroke mortality in blacks. Disturbing trends. *Stroke* 1999;30:1711-1715.
- 14 Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO: Stroke incidence, prevalence, and survival: Secular trends in Rochester, Minnesota, through 1989. *Stroke* 1996;27:373-380.
- 15 Wolf PA, D'Agostino RB: Secular trends in stroke in the Framingham Study. *Ann Epidemiol* 1993;3:471-475.
- 16 Kissela B, Schneider A, Kleindorfer D, Khoury J, Miller R, Alwell K, Woo D, Szaflarski J, Gebel J, Moomaw C, Pancioli A, Jauch E, Shukla R, Broderick J: Stroke in a biracial population: The excess burden of stroke among blacks. *Stroke* 2004;35:426-431.
- 17 Schoenfeld DA: Sample-size formula for the proportional-hazards regression model. *Biometrics* 1983;39:499-503.
- 18 The Atherosclerosis Risk in Communities (ARIC) Study: Design and objectives. The ARIC investigators. *Am J Epidemiol* 1989;129:687-702.
- 19 Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A, et al: The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1991;1:263-276.
- 20 Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP: Multi-ethnic study of atherosclerosis: Objectives and design. *Am J Epidemiol* 2002;156:871-881.
- 21 Ware J Jr, Kosinski M, Keller SD: A 12-item short-form health survey: Construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220-233.
- 22 Berkman LF, Syme SL: Social networks, host resistance, and mortality: A nine-year follow-up study of Alameda County residents. *Am J Epidemiol* 1979;109:186-204.
- 23 Jones WJ, Williams LS, Meschia JF: Validating the Questionnaire for Verifying Stroke-Free Status (QVSFS) by neurological history and examination. *Stroke* 2001;32:2232-2236.
- 24 Orme JG, Reis J, Herz EJ: Factorial and discriminant validity of the Center for Epidemiological Studies Depression (CES-D) scale. *J Clin Psychol* 1986;42:28-33.
- 25 Cohen S, Kamarck T, Mermelstein R: A global measure of perceived stress. *J Health Soc Behav* 1983;24:385-396.
- 26 Callahan CM, Unverzagt FW, Hui SL, Perkins AJ, Hendrie HC: Six-item screener to identify cognitive impairment among potential subjects for clinical research. *Med Care* 2002;40:771-781.
- 27 Cushman M, Cornell ES, Howard PR, Bovill EG, Tracy RP: Laboratory methods and quality assurance in the Cardiovascular Health Study. *Clin Chem* 1995;41:264-270.
- 28 Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L: A data-based approach to diet questionnaire design and testing. *Am J Epidemiol* 1986;124:453-469.
- 29 Rautaharju PM, Park LP, Chaitman BR, Rautaharju F, Zhang ZM: The Novacode criteria for classification of ECG abnormalities and their clinically significant progression and regression. *J Electrocardiol* 1998;31:157-187.
- 30 Prineas RJ, Blackburn H, Crow RS: The Minnesota Code Manual of Electrocardiographic Findings: Standards and Procedures for Measurement and Classification. Boston, Wright-PSG, 1982.

- 31 The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 6 report. *Arch Intern Med* 1997;157:2413–2446.
- 32 National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Circulation* 2002;106:3143–3421.
- 33 Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS: Comparison of diabetes diagnostic categories in the U.S. population according to the 1997 American Diabetes Association and 1980–1985 World Health Organization diagnostic criteria. *Diabetes Care* 1997;20:1859–1862.
- 34 Wagenknecht LE, Mayer EJ, Rewers M, Haffner S, Selby J, Borok GM, Henkin L, Howard G, Savage PJ, Saad MF: The Insulin Resistance Atherosclerosis Study (IRAS) objectives, design, and recruitment results. *Ann Epidemiol* 1995;5:464–472.
- 35 Chambless LE, Toole JF, Nieto FJ, Rosamond W, Paton C: Association between symptoms reported in a population questionnaire and future ischemic stroke: The ARIC study. *Neuroepidemiology* 2004;23:33–37.
- 36 Spence JD, Howard VJ, Chambless LE, Malinow MR, Pettigrew LC, Stampfer M, Toole JF: Vitamin Intervention for Stroke Prevention (VISP) trial: Rationale and design. *Neuroepidemiology* 2001;20:16–25.
- 37 Lefkowitz DS, Brust JCM, Goldman L, Johnson JL, Toole JF, Howard V, Chambless L: A pilot study of the end point verification system in the Asymptomatic Carotid Atherosclerosis Study. *J Stroke Cerebrovasc Dis* 1992;2:92–99.
- 38 Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE III: Classification of subtype of acute ischemic stroke: Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;24:35–41.
- 39 Kasner SE, Cucchiara BL, McGarvey ML, Luciano JM, Liebeskind DS, Chalela JA: Modified National Institutes of Health Stroke Scale can be estimated from medical records. *Stroke* 2003;34:568–570.
- 40 Elkind MS, Cheng J, Boden-Albala B, Paik MC, Sacco RL: Elevated white blood cell count and carotid plaque thickness: The Northern Manhattan Stroke Study. *Stroke* 2001;32:842–849.
- 41 Cooper ES: Cardiovascular diseases and stroke in African Americans: A call for action. *J National Med Ass* 1993;85:97–100.
- 42 Census 2000 Summary File 1, Technical Documentation, Prepared by the U.S. Census Bureau, Washington, 2001.