The Sleep Heart Health Study: Design, Rationale, and Methods

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Summary: The Sleep Heart Health Study (SHHS) is a prospective cohort study designed to investigate obstructive sleep apnea (OSA) and other sleep-disordered breathing (SDB) as risk factors for the development of cardiovascular disease. The study is designed to enroll 6,600 adult participants aged 40 years and older who will undergo a home polysomnogram to assess the presence of OSA and other SDB. Participants in SHHS have been recruited from cohort studies in progress. Therefore, SHHS adds the assessment of OSA to the protocols of these studies and will use already collected data on the principal risk factors for cardiovascular disease as well as follow-up and outcome information pertaining to cardiovascular disease. Parent cohort studies and recruitment targets for these cohorts are the following: Atherosclerosis Risk in Communities Study (1,750 participants), Cardiovascular Health Study (1,350 participants), Framingham Heart Study (1,000 participants), Strong Heart Study (600 participants), New York Hypertension Cohorts (1,000 participants), and Tucson Epidemiologic Study of Airways Obstructive Diseases and the Health and Environment Study (900 participants). As part of the parent study follow-up procedures, participants will be surveyed at periodic intervals for the incidence and recurrence of cardiovascular disease events. The study provides sufficient statistical power for assessing OSA and other SDB as risk factors for major cardiovascular events, including myocardial infarction and stroke. **Key Words:** Sleep apnea—Cardiovascular disease—Epidemiology—Risk factors.

Obstructive sleep apnea syndrome (OSA) is a potentially debilitating condition characterized by repetitive episodes of apnea while asleep, nocturnal oxygen desaturation, excessive daytime sleepiness, and loud disruptive snoring (1). Recent epidemiologic data from middle-aged adults indicate that OSA is common, with prevalence rates of 4% in men and 2% in women (2). Several studies have implicated OSA as a risk factor

for the development of hypertension (3), ischemic heart disease (4), congestive heart failure (5), stroke, and consequently premature death (6). Nevertheless, these data are limited and the need for additional investigation into the natural history and cardiovascular consequences of OSA has been stressed (7).

It is unclear whether an increased propensity for cardiovascular and cerebrovascular diseases is limited to only those with frank OSA or whether more subtle forms of sleep-disordered breathing (SDB) also confer risk. Furthermore, SDB, including OSA, may not be an independent risk factor for the development of cardiovascular or cerebrovascular disease. Known cardiovascular and cerebrovascular disease risk factors such as obesity and smoking commonly are present in those with SDB. Therefore, the apparent associations be-

tween SDB and cardiovascular and cerebrovascular diseases may only result from the effects of these concomitant risk factors. Moreover, there is no understanding as to whether such factors as race, age, gender, and prevalent cardiovascular or cerebrovascular disease might interact with SDB to alter future cardiovascular and cerebrovascular disease risk. Mechanisms underlying any propensity to develop cardiovascular or cerebrovascular disease with SDB also have not been firmly established.

Although an ideal study of the cardiovascular consequences of sleep apnea might be designed to follow a cohort of young adults with repetitive assessment of SDB and monitoring for incident cardiovascular and cerebrovascular events, substantial resources and length of follow-up would be required. Alternatively, the Sleep Heart Health Study (SHHS) attempts to exploit the power of a classic longitudinal study and the feasibility of cross-sectional studies by enrolling middle-aged and older participants who have had previous risk factor data collected in other studies to prospectively assess new or recurrent cardiovascular and cerebrovascular diseases and their relationship to SDB defined at one point in time. The principal objective of the SHHS is to determine whether SDB, including OSA, is an independent risk factor for the development of cardiovascular and cerebrovascular diseases. This paper outlines the study design and methods.

STUDY DESIGN AND METHODS

Primary hypothesis of SHHS

The primary hypothesis to be tested in SHHS is that sleep-disordered breathing is associated with an augmented risk of incident coronary heart disease (CHD) events, incident stroke, longitudinal increase in blood pressure, and all-cause mortality.

Study design

The SHHS is designed as a prospective cohort study. Although SHHS has a recruitment goal of 6,600 subjects, power calculations were based on a target sample size of 6,000 participants. It is expected that approximately one-third of this sample will have prevalent cardiovascular or cerebrovascular disease on enrollment, leaving 4,000 subjects at risk for incident events. For a sample of this size, an event rate of 1.5%, and OSA prevalence of 25% (2,8), there is approximately 70% power to detect a relative risk of 2.0 at the 5% significance level over a projected 2 years of average follow up. Higher incidence rates (achievable after longer follow-up) and prevalence rates or relative risks yield power estimates above 80%.

A comprehensive description of the methods used in the study is contained in the *SHHS Manual of Operations* (9). The overall approach includes recording a polysomnogram to measure sleep and SDB in all participants. To be eligible, individuals must be 40 years of age or older at the time of their sleep study. Data pertaining to cardiovascular risk factors and sleep habits will be obtained for all participants shortly before or after their enrollment in SHHS. There will be follow-up at periodic intervals for cardiovascular and cerebrovascular mortality and morbidity.

A new cohort is not being recruited for SHHS; rather, SHHS draws participants from established cohort studies principally directed at cardiovascular diseases in several ethnic groups. SHHS adds the assessment of sleep and sleep-disordered breathing to the protocols of these studies. This approach has the advantage of feasibility and cost effectiveness. Other than measures of sleep and SDB, most of the predictor and outcome measures have been or will have been collected for each participating cohort as part of their ongoing data collection efforts using previously established methodology. The availability of data on cardiovascular and cerebrovascular disease risk factors obtained prior to the collection of information pertaining to sleep and SDB also affords the opportunity to model potentially complex interactions between rate of change in these risk factors and SDB. Furthermore, the selection of subjects from among established participants in ongoing longitudinal studies may enhance enrollment rates.

Description of parent cohorts and recruitment objectives

Atherosclerosis Risk in Communities Study (ARIC)

ARIC was started in 1986 with the overall objective of prospectively investigating the etiology and natural history of atherosclerosis and the etiology of clinical and subclinical atherosclerosis in four communities across the United States (10). Participants between the ages of 45 and 64 years were recruited between December 1986 and December 1989. By 1995, the cohort age range was approximately 52–73 years. ARIC participants are contacted annually via telephone and undergo examinations every 3 years to identify and assess cardiovascular risk factors and mortality and morbidity endpoints. The fourth examination of this cohort is currently being conducted. Two ARIC cohorts participate in the SHHS: suburban Minneapolis, MN, and Washington County, MD.

The Minnesota ARIC cohort initially consisted of 4,009 men and women who were recruited between 1987 and 1989 from eight contiguous suburbs of Min-

neapolis, MN, and who were selected from Hennepin County's jury selection list. The characteristics of this cohort reflect the eligible population in the suburban Minneapolis area selected. Of 3,497 participants in the 1992–95 exam, approximately one-half were women (52%), and 99% of the cohort was white. SHHS intends to recruit 1,000 Minnesota ARIC participants.

The Washington County ARIC cohort initially consisted of 4,020 men and women recruited between 1987 and 1989 using a private census conducted by the Johns Hopkins Training Center in 1975 and driver's license records (10). Of the 3,425 eligible participants in the 1993–95 exam, 46% were men and 99% were white. SHHS intends to recruit 750 Washington County ARIC participants.

Cardiovascular Health Study (CHS)

CHS started recruitment in June 1989 with the overall objective of identifying risk factors for coronary heart disease and stroke in adults (11). Three of the four clinical centers of the CHS are participating in the SHHS (Allegheny County, PA; Sacramento County, CA; and Washington County, MD). Participants in CHS are evaluated annually at the participating clinics to identify and assess cardiovascular risk factors and to perform special examinations such as carotid ultrasounds and echocardiograms. Procedures for identifying mortality and morbidity endpoints also have been implemented.

As of November 1, 1995, the Sacramento County cohort consists of 1,341 participants, of whom 41% are men, 80% are white, and 17% are African-American. The Allegheny County cohort comprises 1,287 participants, of whom 42% are men, 77% are white, and 22% are African-American. The Washington County cohort consists of 1,065 participants, of whom 40% are men and 99% are white. SHHS intends to recruit 500 individuals from both the Sacramento County and Allegheny County sites and 350 from the Washington County site.

Framingham Heart Study (FHS)

Subjects for the SHHS are being recruited from two cohorts of the FHS: the Offspring cohort and the Omni cohort. The original cohort of the Framingham Heart Study, recruited in 1948, was a sample of 5,209 men and women aged 30–62 years, including 1,644 husband and wife pairs (12). The children of these 1,644 couples plus the children of 378 original cohort members with heart disease, and their spouses, were later invited to participate in the study. The resulting Offspring cohort initially included 5,124 men and women,

and its examination began in 1971. There are 4,660 active members of the cohort, of whom 45% are men and 99% are white. Recruitment of the Omni cohort began in 1994 and is ongoing. This cohort consists of Framingham, MA, residents aged 40–74 years who describe themselves as members of a minority group. Recruitment for this cohort has employed a multimodality approach to invite all age-eligible minority residents to participate. As of September 20, 1996, 260 new subjects have undergone an initial examination identical to that of the Offspring cohort. The SHHS intends to enroll 1,000 participants from the FHS, of whom 30% will be from the Omni cohort.

New York cohorts

The New York cohorts consist of three study populations participating in a program project entitled "Psychosocial Factors and Cardiovascular Disease" (13,14). In the first cohort (clinic study), subjects were recruited from the Cornell University Medical Center Hypertension Center and Harlem Hospital Hypertension Clinics in New York City, with normal volunteers acting as controls for the hypertensive subjects. There are two components of the Clinic Study. The first is a long-term (up to 20 years) follow-up study of a cohort of 2,777 patients, enrolled between 1978 and March 1992, who have worn an ambulatory blood pressure monitor. The primary aim of this component is to determine whether ambulatory blood pressure monitoring is a better measure of cardiovascular risk than traditional clinic blood pressure measurements. The second component is a cross-sectional comparison of ambulatory blood pressures and associated risk factors in samples recruited from the Cornell and Harlem hypertension clinics since March 1992. The focus of this component is a comparison between the two recruitment sites of normotensive individuals and patients with uncomplicated hypertension. As of June 1995, 1081 SHHS-eligible participants have been enrolled in this cross-sectional component, of whom 44% are men, 80% are white, and 14% are African-American. They range in age from 40 to 79 years.

The second cohort (Worksite) is a population of volunteers employed at 10 worksites around New York City participating in a study evaluating the relationship of occupational stress to blood pressure. Worksite subjects are recruited from randomly selected employees meeting the criteria of normotension or borderline hypertension at entry. There are 422 SHHS-eligible Worksite cohort participants, of whom 64% are men, 66% are white, and 23% are African-American. Their ages range from 40 to 69 years. The third cohort (Menopause) is a small group of perimenopausal women, 35 years of age or older, currently being recruited to

study blood pressure and hormonal changes occurring in association with the menstrual cycle and menopause. Of a projected enrollment of 90 subjects, 75 will be over the age of 40 and thus eligible for participation in SHHS. Of the women already recruited, 47% are white, 32% are African-American, 16% are Hispanic, and 5% are Asian-American.

All three projects involve a full cardiovascular evaluation at enrollment, which includes a 24-hour recording of ambulatory blood pressure. Follow-up of patients includes assessments of blood pressure, medication use, and morbid events. Follow-up of the Worksite subjects involves full reevaluations every 3 or 4 years. The SHHS intends to enroll 1,000 participants from the New York cohorts.

Strong Heart Study (SHS)

The SHS began in 1989 with the principal objective of estimating cardiovascular disease mortality and morbidity rates and comparing cardiovascular disease risk factors among Native Americans residing in three areas (15). The study population included members of the following tribes between 45 and 74 years of age: 1) Pima, Maricopa, and Tohono O'odham (Papago) of central Arizona (residing in the Gila River, Salt River, and Ak-Chin communities); 2) the seven tribes of southwestern Oklahoma (Apache, Caddo, Comanche, Delaware, Fort Sill Apache, Kiowa, and Wichita); and 3) the Oglala and Cheyenne River Sioux in South Dakota and the Spirit Lake Sioux in the Fort Totten area of North Dakota. Participants undergo periodic evaluations to identify and assess cardiovascular risk factors and to determine mortality and morbidity endpoints. Two SHS examinations have been completed, with the third scheduled to begin in 1998.

There are 4,549 participants in the SHS, of whom 41% are men. Their ages range between 48 and 81 years. SHHS intends to recruit 200 Native American subjects from each of the three study areas of the SHS.

Tucson Cohorts

The Tucson cohorts consist of two study populations participating in a Specialized Center of Research program entitled "Chronic Diseases of the Airways". The first cohort is the Tucson Epidemiologic Study of Airways Obstructive Diseases (TES), which is a longitudinal population-based study designed to investigate the etiology and natural history of airways obstructive diseases (AOD) (16). It is a random, multistage stratified sample of the white, non-Hispanic population of Tucson, AZ. Initial enrollment occurred between 1971 and 1973 and was stratified to ensure sufficient sam-

pling of individuals with low socioeconomic status and the elderly. The current study population consists of those initially recruited and subsequent enrollment of new household members (e.g. spouses and newborns). Twelve surveys of the population have been completed, with data obtained pertaining to respiratory and cardiovascular disease risk factors and mortality and morbidity endpoints. There are 1,201 members of the cohort over the age of 40 years, of whom 43% are men and 96% are white. The second cohort is the Tucson Health and Environment Study (H&E). This population is a multistage stratified cluster sample drawn in 1987 and 1988 from the municipal employees of Pima County, in which Tucson is located (17,18). The objective of this study is to evaluate the role of bronchial responsiveness, host immunological status, smoking, and environmental and occupational exposures in the etiology and natural history of AOD. This population has undergone periodic health evaluation surveys similar to the TES. There are 920 members of the H&E cohort eligible for the SHHS, of whom 47% are men, 81% are white, and 13% are Hispanic. The SHHS intends to recruit 900 participants from the combined TES and H&E cohorts.

Sampling and recruitment plan

Recruitment of the projected 6,600 participants in SHHS initially will be based on the following sampling priorities and inclusion/exclusion criteria.

1. Participants will be at least 40 years of age. Excluding young individuals with low risk for developing cardiovascular disease will increase the rate of incident disease in the study population.

2. Individuals with sleep apnea that has been treated with continuous positive airway pressure or oral devices, persons using home oxygen therapy, and persons who have had tracheostomy will be excluded. Performing home polysomnograms on these individuals can present technical difficulties. In addition, treatment may alter their risk of developing subsequent cardiovascular disease.

3. Approximately equal numbers of men and women will be recruited. This will allow the study objectives to be applied to both genders.

4. Priority will be given to recruitment of ethnic minorities. To have a study population that embodies the multiethnicity of the United States, minority participants will be preferentially recruited. It is projected that the total number of minority participants will be approximately 1,400.

5. Habitual snorers will be oversampled in cohorts recruiting subjects younger than age 65 years. This will enrich the sample of younger subjects, in whom the presence of snoring increases OSA risk by 3–10

TABLE 1. *Comparability of variables from parent cohorts according to SHHS priority level*

A variables	Maximum window for A variables	B variables	C variables
Categorical covariates			
Prevalent cardiovascular disease	3 months	Noncardiopulmonary medical history	
Prevalent myocardial infarction		Family history of CVD	
Prevalent stroke		Parental	
Angina		Sibling	
Congestive heart failure		Occupation	
Self-reported hypertension	3 years	Psychosocial status	
Self-reported diabetes	3 years	Access to health care	
Self-reported respiratory symptoms	3 months		
Self-reported history of SDB	3 months		
Cigarette smoking status	3 months		
Educational level	Any		
Marital status	3 years		
Race	Any		
Gender	Any	.	
Continuous covariates			
Age	Current	Hemostasis parameters	Passive smoking
Cigarettes/day	3 months	Fibrinogen	Diet
Cigarette × years	3 months	Factor VII	Caloric intake
Usual alcohol intake	3 years	Physical activity	Fat intake
Usual caffeine intake	3 months	Family income level	Antioxidants
Seated blood pressure	Current		
Anthropometric indices			
Height	Any		
Weight	1 month		
Waist, hip girths	3 years		
Neck girth	Current		
Total cholesterol	3 years		
High-density lipoprotein cholesterol	3 years		
Triglycerides	3 years		
Spirometry	5 years		
Ankle-arm index	Any		
Other			
Medications	Current	Echocardiography	24-hour blood pressure
Electrocardiogram	3 years		Holter
			MRI

SHHS, Sleep Heart Health Study; CVD, cardiovascular disease; SDB, sleep-disordered breathing; MRI, magnetic resonance imaging.

fold (19), with subjects having increased levels of SDB. Oversampling of older snorers will not be conducted because of the suspected high prevalence of OSA in random samples of the elderly (8) and potential weaker relationships between self-reported snoring and OSA in older individuals (20). In addition, oversampling of snorers will not occur if participation rates in a cohort are not high enough to exclude some non-habitual snorers from enrollment.

6. Prevalent cardiovascular disease and hypertension will not be excluded. Although this will result in fewer incident cases, SHHS will be able to determine whether those with prevalent disease are at different risk for subsequent cardiovascular disease than those without disease. Moreover, cross-sectional analyses with CHD prevalence as the outcome will be possible.

Generally, participants will be recruited through targeted mailings and telephone calls and during clinic visits for examinations being conducted by their parent

cohorts. The recruitment techniques are necessarily cohort specific, as described in the *SHHS Manual of Operations* (9). Enrollment of participants began December 1, 1995, and will continue for 24 months.

Data acquisition

Comparability of information from parent cohorts

A distinctive feature of SHHS is the use of existing data from the parent cohorts to achieve its objectives. In protocol development, it was considered crucial to compare each parent cohort's methods of data collection on variables considered critical for the study's objectives. For this purpose, potential variables were prioritized as follows (Table 1): A-variables critical for the primary objectives of the study (if any of the cohorts do not have comparable data for any of these variables, additional data are collected); B-variables

for specific or subset analyses (an attempt to achieve comparability will be made, but it is not required that all cohorts have comparable information); C-variables for cohort-specific analyses or ancillary studies (no specific attempt to achieve comparability will be made).

The A-variables include those needed to define prevalent clinical and subclinical cardiovascular disease as well as the main cardiovascular risk factors previously described as strong correlates of SDB (hypertension, smoking, anthropometric indices). Other cardiovascular risk factors that have not been clearly identified as correlates of SDB are also included, to study their role as possible confounders or effect modifiers. Finally, the list of A-variables includes medications and other strong correlates or indicators of respiratory or sleep disorders (self-reported history of SDB and respiratory symptoms, caffeine and alcohol intake, spirometry). For each of the A-variables, a maximum acceptable time window between the time of the home polysomnogram and the closest measurement is specified (Table 1). A comparability study was performed on the A-type variables to determine whether each parent cohort had the data required in a format that could be combined with those of all SHHS cohorts and to determine whether statistical adjustments would be required in subsequent analyses in data from some of the parent cohorts. As a result of this study, some of the A-variables not uniformly collected across all sites are included in the SHHS protocol for data collection. Other additions to the SHHS protocol are cohort specific, such as collection of spirometry data for the New York cohorts.

Sleep habits questionnaire

The SHHS sleep habits questionnaire was developed to serve four main purposes: 1) to ascertain snoring status in potential participants to facilitate oversampling of habitual snorers in those parent cohorts with younger participants; 2) to identify potential participants who should be excluded from participation (vide supra, Sampling and Recruitment); 3) to obtain data pertaining to sleep habits and symptoms from SHHS participants which are not available from the parent cohorts; and 4) to collect information pertaining to self-reported sleep habits from a very large sample (>20,000). It is planned that the sleep habits questionnaire will be administered to all members of the parent cohorts, irrespective of participation in SHHS. Items on the sleep habits questionnaire were adapted from those used in other surveys of sleep in large populations (2,18,21) and are described in the SHHS Manual of Operations (9). In all cohorts, self-completion of the sleep habits questionnaire is generally performed

several weeks before or at the time of the home polysomnogram.

Home polysomnogram examination

Participants are scheduled for a home polysomnogram as soon as possible after recruitment. In a few cases, recordings are performed in a nonhome environment such as a motel room because the home environment is not conducive to a technically acceptable recording (i.e. extreme heat during the summer and the absence of air conditioning). Data collected during the home examination include the following: seated blood pressure, weight, neck circumference, health interview (questions pertaining to prevalent cardiovascular and respiratory disease and smoking), current medications, quality of life questionnaire (SF-36), modified Epworth sleepiness scale, morning sleep quality survey, and home polysomnogram.

Nonpolysomnographic components. Current medication usage is ascertained using the survey instrument developed for the CHS (22). A standardized quality of life instrument (SF-36) (23) and a modified version of the Epworth sleepiness scale also are administered (24). The latter was validated against the original scale in a pilot study and was found to give highly comparable results. Additional data pertaining to cardiovascular risk factors are obtained by structured interview. In some cohorts, cohort-specific questions are asked because certain data items were not available from the parent study (9). For example, questions to assess educational level were added to the home interview in Framingham. On the morning after the polysomnogram, a questionnaire is administered to assess sleep quality during the night of the recording.

Triplicate measurements of sitting blood pressure are measured in the right arm after a 5-minute rest using an appropriate sized blood pressure cuff and a conventional mercury sphygmomanometer. The average of the second and third readings is used for analysis (9). Weight and neck circumference also are obtained at the time of the home polysomnogram (9).

Home polysomnography. The Compumedics P Series System (Abbotsford, Victoria, Australia) was selected as the primary data acquisition tool because of its portability and capability of recording a full polysomnographic montage, sampling (up to 500 Hz), storage capacity (20–40 megabytes), and the flexibility of its software. This system consists of a Patient Interface Box (PIB "headbox") containing amplifiers and filters to which electrodes and sensors are connected. The PIB is attached by a cable to an 835 g data acquisition recorder containing a computer (PCMCIA card), a 15-hour rechargeable battery, and an oximeter. The PIB and loose electrode wires and sensor cables are sup-

ported by a cloth "bib" that is placed over the participants' nightclothes.

Sensors are placed and equipment is calibrated during the evening home visit. The following channels are recorded: electroencephalogram (EEG) (C3A2 and C4A1), electrooculogram, chin electromyogram, thoracic and abdominal displacement (inductive plethysmography bands), airflow (nasal-oral thermocouples), finger pulse oximeter, a single bipolar electrocardiogram, body position by an Hg gauge sensor, and ambient light level. Snoring was not recorded because of difficulty in objectively defining and accurately measuring it.

Data, stored in real time on PCMCIA cards, are reviewed initially at each clinical site and then are transmited to a central polysomnography reading center that was established to provide uniform, standardized scoring and quality assessment determinations for all polysomnographic data. At the reading center, the data are reviewed for technical quality and for evidence of marked abnormalities in breathing, heart rate, and oxygen saturation that may require timely participant notification. With use of computer-assisted scoring, a preliminary report is sent to each site for use in formulating participant feedback letters.

Final scoring is performed manually on an epoch-by-epoch basis. Sleep staging, arousal detection, and marking of hypopneas and apneas are performed using criteria developed by a subcommittee of SHHS sleep specialists and documented in the *SHHS Reading Center Manual of Operations* (25). Scoring of sleep (26) and identification of arousals (27) are performed using standard criteria. Apneas are identified if the amplitude of the airflow or respiratory band signals decreases to below (approximately) 25% of the amplitude of "baseline" breathing (identified during a period of regular breathing with stable oxygen levels) for >10 seconds. Hypopneas are identified if the amplitude of the airflow or respiratory band signals decreases to below (approximately) 70% of the amplitude of "baseline" for >10 seconds. Apneas are considered to be "central" if no effort is noted on either the thorax or abdominal effort channel. All hypopneas are considered "obstructive". Analysis software links each apnea and hypopnea with data from the saturation and EEG channels, allowing each event to be characterized according to the degree of associated desaturation and associated arousals.

Classification of cardiovascular events

The incident cardiovascular events that will be considered as mortality and morbidity endpoints for SHHS are the following: hospitalized acute myocardial infarction, coronary surgical intervention (coronary artery angioplasty, stent placement, and bypass grafting), angina pectoris, coronary heart disease death, any coronary heart disease (a summary variable that includes the preceding four categories), and stroke. Recurrent cardiovascular events include hospitalized acute myocardial infarction, coronary surgical intervention, and stroke. For the Framingham, ARIC, CHS, and SHS cohorts, ascertainment and adjudication of incident and recurrent events and classification of prevalent disease will be performed by the parent cohorts. The validity of this approach was demonstrated by performing a pilot comparability study for hospitalized acute myocardial infarctions in which nearly uniform agreement was observed between parent cohort classification and a group of SHHS investigators. For the Tucson and New York cohorts, interval follow-up will be performed using procedures and questionnaires modified from the ARIC and CHS (10,11), and classification of new events and prevalent disease will be accomplished using procedures developed for the CHS (11).

DISCUSSION

The SHHS is a prospective cohort study designed to determine if SDB, including OSA, is a risk factor for cardiovascular and cerebrovascular diseases. Recruiting SHHS participants from existing cohort studies, instead of recruiting a new cohort solely for the objectives of SHHS, has greatly reduced the costs of the study, but the design does deserve careful consideration of possible selection biases. The original cohorts were recruited at particular response rates, and participants for the SHHS are being recruited from surviving members of the cohorts, who will not necessarily be representative of the original participants in the parent cohorts. Those choosing to participate in SHHS may be more likely to have sleep problems or to be concerned about cardiovascular health. Nevertheless, these potential effects should not compromise the internal validity of the study. Moreover, there is no definitive evidence that these factors are risks for incident cardiovascular and cerebrovascular diseases. Furthermore, any possible impact of these factors will be assessed using data from the parent cohorts on participants and nonparticipants and on the characteristics of those who survived from the original recruitment to the time window during which SHHS participants are enrolled.

The study elected to exclude individuals from participation if they had OSA and were using continuous positive airway pressure, mandibular repositioning devices, oxygen, or had undergone tracheostomy for sleep apnea. This decision was made because studies indicate that some of these treatment modalities may

alter any excess risk of developing cardiovascular disease conferred by OSA (28,29). Thus, cardiovascular mortality and morbidity results might be confounded by inclusion of such individuals. Although exclusion might introduce other biases, this is unlikely, inasmuch as preliminary analysis of ~10,000 individuals indicates that only 10 potential participants, or 0.1%, have been excluded by virtue of continuous positive airway pressure usage; exclusion rates for other therapeutic modalilties also were <1% each.

There are several other advantages to the SHHS design. Because of the availability of data pertaining to cardiovascular and cerebrovascular disease risk factors in the parent cohorts, SHHS has the potential of addressing several other issues related to SDB, such as whether SDB is associated with increases in left ventricular mass or whether SDB promotes hypercoagulation and thrombosis. In addition, the possibility of performing targeted substudies of some of the SHHS cohort participants provides the opportunity of investigating possible mechanisms underlying cardiovascular and cerebrovascular risk from SDB. Furthermore, as a result of using ambulatory monitoring to examine these participants, it will be possible to make inferences pertaining to the feasibility of using home monitoring to acquire sleep and respiratory data in clinical settings.

In addition to overall summary measures describing the amount of SDB in rapid eye movement and non-rapid eye movement sleep and according to body position, the full polysomnographic montage used in SHHS will permit characterization of the degree of sleep fragmentation. Repetitive transient arousals may promote oscillations in blood pressure and an increase in sympathetic nervous system output (30). This may increase cardiovascular and cerebrovascular risk. The availability of measurements of sleep fragmentation will permit conclusions to be drawn concerning the role of transient arousal, in addition to SDB and oxygen desaturation events, on the pathogenesis of cardiovascular and cerebrovascular diseases in this cohort. Studying subjects over a wide spectrum of SDB also may allow assessment of which physiological correlates (measured by polysomnography) are most strongly linked to SDB and cardiovascular or cerebrovascular diseases, and whether there is a "threshold" level of SDB that predicts morbidity and mortality.

To date, SHHS is the only prospective longitudinal investigation of this magnitude designed to determine whether OSA is a risk factor for cardiovascular and cerebrovascular diseases in the general population. As a consequence, the study will provide important information concerning the burden of morbidity and mortality caused by OSA.

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APPENDIX

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