NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE ON AGING
INTRAMURAL RESEARCH PROGRAM

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LAY SUMMARY:

The National Institute on Aging (NIA) Intramural Research Program (IRP) has been long interested in the cellular and molecular mechanisms of normative aging and age-related disease development. The program has pursued basic laboratory and longitudinal clinical research in normative aging to address these interests. NIA

intramural investigators have expanded the program's capacity to address hypotheses about aging and health disparities in minority and poor populations. By posing fundamental questions about differences in rates and risks for pathological conditions associated with aging, studying groups with diverse racial, ethnic, and economic origins, IRP clinical researchers hope to understand the significance of environmental and genetic risk factors for disease. The need to understand the driving factors behind persistent black-white health disparities in overall longevity, cardiovascular disease, and cerebrovascular disease, has led to the effort to develop and plan the NIA IRP *Healthy Aging in Neighborhoods of Diversity Across the Life Span* (HANDLS) study is a community-based, epidemiologically driven research effort designed to focus on evaluating health disparities in socioeconomically diverse African Americans and whites in Baltimore. This study is unique because it is a multidisciplinary project that assesses physical parameters as well as evaluating genetic, biologic, demographic, psychosocial, and psychophysiological parameters of Black and White participants in higher and lower socioeconomic status (SES) over a 20-year period. It also employs novel research tools, mobile medical research vehicles to improve participation rates and retention among non-traditional research participants. The initial examination and recruitment phase will take approximately 3 years to complete. The study data will be collected in two parts. The first part consists of an in-home interview that includes questionnaires about the participant's health status, health service utilization, psychosocial factors, nutrition, neighborhood characteristics, and demographics. The second part will be collected on the medical research vehicles and includes medical history and physical examination, dietary recall, cognitive evaluation, psychophysiology assessments including heart rate variability, arterial thickness, carotid ultrasonography, assessments of muscle strength and bone density, and laboratory measurements (blood chemistries, hematology, biomarkers of oxidative stress and biomaterials for genetic studies).

Objectives and Aims

The primary objective of HANDLS is to conduct a longitudinal study of minority health focused on investigating the differential influences of race and socioeconomic status on health in an urban population.

The scientific research questions for this multidisciplinary epidemiologic study of minority health and health disparities are:

- Do race and SES influence health disparities independently or do they interact with several factors (race, environmental or biologic factors, and cultural or lifestyle practices)?

- What is the influence of SES and race on age-related declines in function in an urban population?

- What is the influence of SES and race on the incidence and natural history of age-related disease?

- Are there early biomarkers of age-related health disparities that may enhance our ability to prevent or ameliorate the severity of these diseases?

For specific systems we will test the following hypotheses:

Cardiovascular – There will be significantly greater decline in cardiovascular health status as a function of SES and race independent of the effects of age in both men and women. For example:

- Intimal medial thickness is greater in African Americans than whites and is greater in African Americans of lower SES as compared to age-matched African Americans with higher SES, in both men and women;

- Vascular stiffness, as assessed by pulse wave velocity, will be greater in African- Americans with low SES, as compared to age-and gender-matched African- Americans with higher SES.

Body Composition and Bone Quality – African Americans have higher lean mass, bone density and fat mass than corresponding groups of white adults. For example:

- African Americans will exhibit a higher rate of loss of muscle mass, accumulation of fat mass and decline in bone density, relative to white adults.

Cognition – The rates of decline of various cognitive abilities will be the same in all groups regardless of race, ethnicity, or SES.

Autonomic Functioning

- Baseline heart rate variability (HRV) is associated with performance on tests of the susceptibility to attentional interference and to tests of affect recognition;

- Increasing HRV during testing predicts greater accuracy on the attentional interference and affect recognition tasks;

- Declines in HRV predict cardiovascular and cerebrovascular morbidity and mortality.

- Differences in HRV explain racial but not socioeconomic differences in hypertension.

Muscle Strength

- African Americans will exhibit better preservation of muscle strength into older ages than other ethnic and racial groups;

- African Americans have the same trajectory of muscle loss as other ethnic or racial groups after accounting for differences in occupational history, nutrition, and body mass and composition;

- All ethnic and racial groups will show the same relationships among changes in muscle strength, physical activity, and cardiovascular fitness regardless of socioeconomic factors, nutrition, and comorbid conditions such as diabetes.

- The greater strength reductions at older ages among lower SES individuals will be attributable to their greater severity of chronic diseases.

Covariates – Other variables such as nutrition, environment and neighborhood effects, genetic make-up, family history, activity level, access to health care, and prevalent medical, dental, psychiatric conditions, oxidative stress, and DNA repair capacity may modulate the effects of SES and race on cardiovascular, musculoskeletal, cognitive, and autonomic functioning. For example:

- The nutritional domain of the study will examine the effects of race socioeconomic status (SES) on nutritional status and identify nutritional factors that may contribute to health disparity in cardiovascular and cerebrovascular health and cognitive function.

- The biomarkers domain of the study will examine possible biologic covariates of health disparities and aging. The early appearance and increased severity of age-associated disease among African Americans and low SES individuals suggests that the factors contributing to the emergence of health disparities may also induce a phenotype of 'premature aging' or 'accelerated aging'. While we do not posit that health disparities result from genetic alterations in genes associated with the known heritable progeroid syndromes. We do hypothesize that in low SES populations with high rates of early onset age-associated disease the interaction of biologic, psychosocial, socioeconomic and environmental factors may result in a phenotype of accelerated aging biologically similar to these syndromes with increased susceptibility to oxidative stress, premature accumulation of oxidative DNA damage, defects in DNA repair and higher levels of biomarkers of oxidative stress. Health disparities therefore, may be the end product of this complex interaction in populations at high risk. HANDLS will examine this hypothesis by measuring biomarkers of oxidative stress including red cell oxidative stress reflected in levels of heme degeneration products and glutathione. Oxidative stress to the genome will be evaluated by assessing levels of the most widely studied oxidative DNA adducts and measuring DNA repair capacity in study participants. Prospectively measuring biomarkers of oxidative stress in a longitudinal study may clarify whether oxidative stress plays a pivotal role in aging and in the development and or progression of age associated disease. It may also provide insights into the different trajectories of aging observed in individuals.

- Epigenetics: The disproportionate incidence and mortality from age-associated disease may also result from epigenetic mechanisms such a DNA methylation. We will examine the hypothesis that human disease and disability may result from DNA modifications that are not the result of a change in the coding sequence of genes. Methylation of CpG islands, associated with stable gene-silencing, has been identified as a causative mechanism in several human disease including cancer, Fragile X and ATR-X syndromes. There is also come evidence to suggest that epigenetic changes play a critical role in the initiation of cellular senescence and in aging. The specific role of methylation in the aging process is unclear. However, studies have shown that CpG methylation and DNA methyl transferase activity decrease with population doublings in normal cells suggesting that methylation might serve as a 'counting mechanism' for senescence. It has also been shown that methylation can repress growth inhibitory genes. This inhibition may decline with increased population doubling resulting in cellular senescence. Supporting this notion is work showing that inhibition of DNA-methyltransferase results in activation of p21.

  The clinical relevance of DNA methylation states in the development of age-related disease has yet to be understood on a population basis. There is variation in methylation states from individual to individual. This may be related to age, gender, environmental exposure, and other genetic factors. Is it possible that our hypothesized phenotype of accelerated aging phenotype seen in low SES and minority communities is related to epigenetic factors such as methylation? We will examine methylation states within this longitudinal cohort to attempt to understand whether methylation states are associated with the premature development of age-associated disease.

Background and Significance

There are well-documented differences in health status among groups defined by age, race, ethnicity, and SES. Over the past decade or so, evidence from cross-sectional studies and nationally representative follow-ups suggests that there are persistent disparities among African Americans and other minority groups compared to Whites in morbidity[1-16] and mortality.[15, 17-22] Double jeopardy describes the constellation of health disparities conferred by old age and membership in a minority group.[23] Evidence suggests that there are unique disadvantages conferred by the combination of old age and minority status,[1-7, 9, 11-20, 23-26] but the extent to which minority status is a direct cause of the disadvantage is unknown. Race, ethnicity, and SES are inextricably confounded in many studies. Membership in a minority group may be an indicator of the combinations of other effects such as low income, poor education, environmental exposure to toxic compounds, and lack of occupational opportunities.

Independent of the effects of race and ethnicity, SES accounts for differences in the functional status associated with chronic disease, but has only a small role in predicting prevalence of chronic disease.[16] Further complicating this relationship, physicians' assessments and treatment differ by race and sex.[24, 27] Addressing these disparities in health status requires data about the differences in risks for chronic disease associated with race, ethnicity, and SES in all groups regardless of their majority or minority standing.

Unfortunately, such studies are rare, not the least because of the difficulty recruiting and retaining subjects in longitudinal follow-ups from some minority and some low SES groups. Surveys of ethnic status and participation in longitudinal health surveys found that African Americans and Mexican Americans were less likely than whites to participate in follow-up surveys.[28] In addition, these minority groups were more difficult to trace over long intervals between interviews. However, difficulties in data collection do not diminish the importance of gathering the information. The National Heart, Lung, and Blood Institute Conference on Socioeconomic Status and Cardiovascular Health emphasized this point by recommending a research agenda focused on:

- promoting the measurement of SES in observational and interventional research using valid and reliable indices, and including such measures as control or stratification variables in data analyses;

- developing well-validated and sophisticated measures of SES for studies of the connection between SES, SES-related daily activities, and CVD, with explicit attention paid to special features conditioning the definition, meaning, and impact of SES in women, minorities, and rural residents; and

- investigating the relationships between SES and CVD onset, progression, prognosis, morbidity, disability, and death with particular attention on measures of preclinical disease (e.g., echocardiography, electrocardiography, sonographic measurement of carotid artery intima-media wall thickness, measurement of ankle-arm blood pressure ratio) and their connection to SES-related exposures.

Although not a direct response to these recommendations, the present proposal captures the spirit of these recommendations by focusing on predictors of change in cardiovascular function and fitness, risks for cerebrovascular conditions such as stroke, vascular dementia, and carotid stenosis, and pathological cognitive decline. We chose these specific areas as representing the health issues that are among the most prevalent, but least understood, in African Americans. Specifically, we will measure carotid arterial blood flow and arterial stiffness by Doppler ultrasonography, muscle strength by grip strength, chair stand and single leg stand exercises, body composition by dual photon x-ray absorptiometry (DXA), and cognitive performance with cognitive and neuropsychological tests.

We will assess each of these areas by separate procedures for which we will investigate cross-sectional differences and longitudinal change within this sample

and by comparison with other samples, particularly the Baltimore Longitudinal Study of Aging (BLSA) with which this study shares many procedures and tests. We will combine these measures in various ways to examine the risks for pathological outcomes such as stroke, dementia, and loss of functional independence.

This protocol focuses primarily on adding minority outreach to our arsenal of longitudinal follow-up studies. We will compare these data to two studies to examine the separate influences of race and SES. The BLSA is an obvious source for many comparisons because we designed the present study to overlap with the BLSA in several key areas. Similarly, the present protocol overlaps with the National Health and Nutrition Examination Survey (NHANES) by using their methods for assessing SES and dietary recall. To the extent that the present data are similar to other data collected by the NHANES, we will compare the present data to their nationally representative data.

There are some advantages in using the BLSA as a comparison group because both studies use the same methods for data collection. Unfortunately, the BLSA has several weaknesses for our purposes. Historically, the BLSA was a study of well-educated upper-middle class White men and women, though women were omitted during the first two decades. More recently, the BLSA has achieved its goals to study equal numbers of men and women, and to expand their recruitment to minorities. Over the past decade, the BLSA has added African Americans who are roughly similar in demographics and SES to their well-educated upper middle-class Whites counterparts. Thus, the BLSA is a useful comparison sample for examining the effects of SES in African Americans on age-related conditions.

There are too few low SES Whites in the BLSA to perform comparisons of health outcomes by SES among Whites. In addition, we are limited to comparisons of Whites with African Americans because the BLSA has insufficient numbers of Latinos. NHANES collects nationally representative data on Latinos, but their data are cross-sectional or rely on indirect follow-up tracking to catalog outcomes. Although NHANES collects more subjects, our protocol focuses on fewer endpoints on which we perform more frequent, in-depth assessments.

In order to fully develop the methodology of this study a pilot phase was developed to address logistical aspects. The pilot phase of this study known as ***Healthy Aging in Nationally Diverse Longitudinal Samples*** **(HANDLS pilot)** used a sample of convenience to evaluate the feasibility of using mobile medical research vehicles as field-based research platforms, tested recruitment and retention techniques, assessed the various research instruments, and developed a detailed logistical plan (e.g., staffing, security, permitting, water access, power supply, telecommunications) for the deployment and movement of the research vehicles.

Wave 1 of HANDLS pilot phase was successful in addressing its primary goal, assessing the feasibility of conducting a community-based study using a mobile medical research vehicle. The first wave of the pilot allowed refinement of the logistical requirements for the conduct of clinical research focused on several scientific and clinical domains among a diverse socioeconomic sample. The second

goal of the first wave of the pilot was to begin to collect data that would expand our understanding about the possible causes of health disparities in the African American community and the effect of race and SES on health and the development of age-related disease and disability. The findings within this cohort from the wave 1 pilot include identification of:

- Increased frequency of depressive symptoms
- Premature increases in intimal medial thickness in carotids
- Genetic polymorphisms implicated in cardiovascular disease have altered frequency
- Decreased muscle strength
- Altered blood pressure and heart rate variability responses to stress and delays in cardiovascular recovery among African Americans
- Significant association between symptoms of depression and cardiovascular reactivity
- Prevalence of obesity

Wave 2 of the pilot phase, currently being conducted in the same West Baltimore neighborhood, will permit further logistical assessments of the mobile medical research vehicle (MRV I) and the newly procured mobile medical research vehicle II (MRV II), evaluation of retention strategies for non-traditional research participants, conduct a 3-year interim follow-up on participants to verify and expand on findings from wave 1 of the pilot and evaluation of new questionnaires and physical assessments to be used in the upcoming epidemiological study. Since February 3, 2003, 244 participants have undergone re-evaluation as part of wave 2. The collection of this important additional data will help to further develop and validate our strategies for retention and re-contact of participants and will facilitate the publication of several manuscripts that will be enhanced by additional data in this sample of convenience.

Study Design

The HANDLS study is a multidisciplinary, prospective epidemiologic longitudinal study examining the influences and interaction of race and SES on the development of cardiovascular and cerebrovascular health disparities among minority and lower SES subgroups.

The baseline HANDLS sample will consist of approximately 4,000 community-dwelling African American and white adults aged 30-64. Participants will be drawn from 12 pre-determined census tracts in Baltimore City, sampling representatively across a wide range of socioeconomic and income circumstances. The heuristic study design is a factorial cross of four factors: age, sex, race, and SES with approximately equal numbers of subjects per “cell.” HANDLS is planned as a 20-year longitudinal study. Using our mobile medical research vehicles, we will visit each census tract for 3 months and we will re-visit every census tract in a 3-year cycle.

The 12 census tracts identified were selected because they are likely to yield representative distributions of individuals between 30 and 64 years old who are African Americans and whites, men and women, and lower and higher SES. Individuals calling themselves multi-ethnics will be included and categorized by the group with which they most strongly identify, but their multi-ethnic identification will be recorded for subsequent statistical analyses. Multi-ethnic individuals who identify strongly with neither African Americans nor whites will be excluded from the present study.

Initial estimates based on the 2000 census data indicate that we will need to visit approximately 35% of the households in each census tract to collect the required 333 individuals. The initial sample of 4,000 participants is based on power analyses and assumptions about attrition over 20 years. For a power of 80% (the likelihood of finding an effect if it is really present), we can identify moderate effects (magnitude of the differences between groups) for various outcomes with as few as 30 participants per group at the end of the study. Working backwards by assuming 20% attrition after the baseline assessment and 15% attrition between subsequent assessments, we need approximately 4,000 participants at baseline to yield 1,680 after 20 years (Figure 1). The recruitment phase and initial examination will take approximately 3 years to complete.

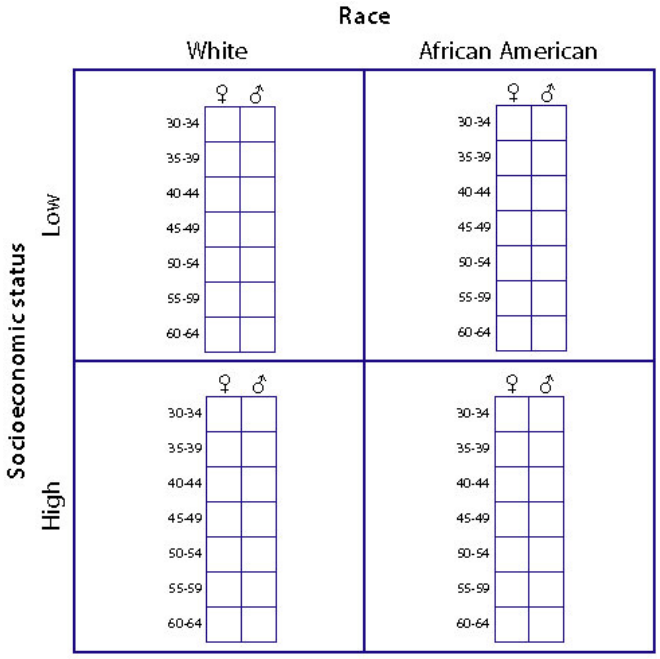

Figure 1. HANDLS sampling design

Methods

The study data will be collected in two parts. The first part of the participant examination is a household interview that will include questionnaires about health status, health services, psychosocial factors, nutrition, neighborhood characteristics, and demographics. The second part of the examination data will be collected on the

medical research vehicles; these include medical history and physical examination, dietary recall, cognitive evaluation, psychophysiology assessments including heart rate variability, arterial thickness, carotid ultrasonography, assessments of muscle strength and bone density, and laboratory measurements (blood chemistries, hematology, biomaterials for genetic studies).

(a) Procedures

The procedures used to collect the data for the HANDLS study will be implemented in two phases:

The first phase is the screening, recruitment and household interview phase. **The second phase** is the Medical Research Vehicle examination phase.

PHASE 1: Screening, Recruitment and Household Interview Phase

The recruitment and sampling contractor will produce household listings for identifying the residential dwellings in each census tract. The contractor will then perform doorstep interviews, identify eligible persons in each household, select one to two eligible persons per household, and invite eligible candidates to participate in HANDLS. Once successfully recruited and consented, they will complete the household survey and dietary recall questionnaire concluding with an appointment for testing on our Mobile Medical Research Vehicles (MRVs).

Household Survey. The household survey inquires about background, demographic information, racial and cultural identification, educational experience, occupational history, family income, total leisure time physical activity, and a wide range of other information broadly conceived as physiological and psychological chronic exposure. The primary purpose for this measure is to characterize the demographic composition of the sample and to serve as covariates in analyses of the primary outcomes.

Risks. None are known.

Dietary Recall. We will ask participants to recall all of the foods and beverages they consumed during the previous 24 hours. An interviewer will record the dietary recall using methods developed by the USDA called the Automated Multiple Pass Method that is supplemented by measurement aids and illustrations to assist in estimating accurate quantities consumed.

Risks. None are known.

PHASE 2: Medical Research Vehicle Examination Phase

The following procedures will be implemented on the MRVs after obtaining informed consent for the second phase of the participant examination:

Medical history and physical examination. A physician or nurse practitioner will perform a comprehensive physical examination and medical history. The purpose of the physical examination and medical history is to document as unambiguously as possible any diagnosable conditions, to record medications and their frequencies and dosages, and to assess disabilities that might limit independent functional activities. In addition, we will examine subjects to insure that they do not meet exclusionary criteria for any subsequent tests such as the DEXA.

Risks. None are known.

Fasting blood samples for List Tests, Banking Plasma, Serum, and DNA. As a part of the medical evaluation, blood tests are performed to look for anemia and other blood disorders, diabetes mellitus, thyroid disease, hepatitis, prostate disease, and kidney disease. We are also using some blood samples to study genes that may play a role in age-related diseases like Alzheimer's disease, heart failure, high blood pressure, and cancer. The total amount of blood drawn from each participant is about 62 milliliters (4½ tablespoons).

Risks. There are some risks from having blood drawn. There is a risk of an infection from the needle puncture. There is also a risk of a black and blue mark, and the participant may feel faint. It is common to have a small black and blue mark, but it disappears after a day or so. Some people may begin to perspire or feel nauseated. These risks are very small. Our medical staff is well trained and has drawn blood many times.

Buccal mucosa smears. As part of the medical evaluation buccal mucosa smears will be collected from each consenting participant using the Whatman FTA collection system. This system collects buccal cells using a foam tipped applicator which is placed into the mouth and rubbed on the inside of both cheeks for 30 seconds by the participant. The sample obtained is then transferred to the Indicating FTA cards. The extracted DNA will be used for epigenetic analysis.

Risks. Buccal Mucosa smear risks include irritation of the inside of the cheek and/or gum line by the foam tipped swab used to collect cells and saliva.

Dietary Recall. This measure will be administered in both phases of data collection. We will ask participants to recall all of the foods and beverages they consumed during the previous 24 hours. An interviewer will record the dietary recall using methods developed by the USDA called the Automated Multiple Pass Method that is supplemented by measurement aids and illustrations to assist in estimating accurate quantities consumed.

Risks. None are known.

Cognitive testing. We will administer a battery of cognitive tests assessing memory, executive function, verbal fluency and knowledge, and spatial ability. In addition to dementia screening using the Mini-Mental State Examination[29], we will administer the Benton Visual Retention Test (BVRT),[30] California Verbal Learning Test,[31] Card

Rotations, Prospective Memory, Wechsler Adult Intelligence Scale Digit Span Forward and Backward,[32] Identical Pictures, Clock Drawing, Brief Test of Attention, Wide Rage Achievement Test, Trail Making A and B, animal fluency. We will assess baseline personality and symptoms of depression using the CES-D.

Risks. None are known.

Audio-administered Questionnaires. We will assess risk of poor mental health and questions about income with a brief audio-administered (using a computer and headphones) psychiatric screen and income questionnaire. Assistance will be provided to the participants, if for example they have trouble seeing or reading the questions or are uncomfortable with using a computer.

Risks. None are known.

Autonomic regulation in aging adults. We will collect data on demographic characteristics and exercise habits. We then will perform non-invasive heart period and blood pressure recordings using the Portapres ambulatory heart rate and blood pressure monitor. Continuous beat-to-beat heart rate and blood pressure data will be collected using a finger cuff placed on the subject's non-dominant hand during this entire section of the protocol. Subjects will complete both a 3-minute anger recall and happy recall task. These tasks involve having the subject recall an event that made them angry and one that made them happy. Before each task we will record a 5 minute baseline. After each task, subjects will be allowed to rest for 10 minutes. Subjects will also stand for 5 minutes (orthostasis) in order to examine the effects of a mild physical challenge. Subjects will complete momentary mood scales at different points in the protocol to assess the underlying role of mood on cardiovascular responses.

Risk. This protocol is completely noninvasive and represents minimal risk to participants.

Carotid Arterial Blood Flow and Arterial Stiffness. Carotid doppler ultrasonography is the method of choice for noninvasive, in vivo examination of the structure and function of the carotid arteries. Intimal-medial thickness has emerged as a potent predictor of stroke,[33-35] myocardial infarction,[35] coronary artery disease,[36] and cardiovascular disease,[34] independent of other traditional cardiovascular risk factors. In this study, we will perform high resolution B-mode ultrasonography on the left carotid artery, for the evaluation of systolic and diastolic common carotid arterial diameters, carotid arterial flow, intimal-medial thickness, and plaques. We will also evaluate the right carotid artery for the presence of plaques.

Risks. None are known

Pulse Wave Velocity (PWV). In addition to arterial wall thickness (IMT), central arterial stiffness is also increasingly recognized as an important predictor of cardiovascular morbidity and mortality.[37-43] Furthermore, recent studies suggest that vascular stiffness may precede the development of hypertension.[44] Thus, vascular

stiffness is emerging as a potent subclinical marker of cardiovascular disease. We propose to non-invasively assess arterial stiffness by measuring central arterial pulse wave velocity. This validated technique involves positioning of Doppler flow probes over the carotid, brachial and femoral pulses, simultaneously recording the waveforms, and gating them to the EKG. The distance between the recording sites is measured externally with a tape measure. Pulse wave velocity between 2 arterial segments is calculated by dividing the distance between the 2 sites by the time delay for the flow waves between these 2 sampling sites.

Risks. None are known.

Bone Density and Body Composition. We will perform dual energy X-ray absorptiometry (DEXA) on total body, lumbar spine, and the hip using a Lunar DPX-IQ (Lunar Corp., Madison, WI). DEXA delivers a small amount of radiation through an X-ray source in a scanning arm while the participant is supine or seated. Site-specific scans of the lumbar spine, right proximal femur, bone area (cm^2), and bone mineral density (g/cm^2). Total body scan measures both body composition and bone mineral density, including bone mineral content (g), bone area (cm^2), bone mineral density (g/cm^2), total body tissue (g), fat mass (g), lean mass (g), lean mass plus bone mineral content (g), and percent total fat (%). Results of the total body scan are presented for the body as a whole as well as for the arms, legs, trunk, head, pelvis, and spine.

Exclusions. DEXA studies are not administered to pregnant women or individuals who have had both hips replaced. Individuals weighing greater than 270 pounds are excluded due to the densitometer's limitations.

Risks. DEXA. The NIH Radiation Safety Committee has reviewed the use of radiation in this research study and has approved this use as involving minimal risk and necessary to obtain the research information desired. Although each organ will receive a different dose, the amount of radiation exposure participants will receive from these procedures is equal to a uniform whole-body exposure of less than 1 millirem. This calculated value is known as the "effective dose" and is used to relate the dose received by each organ to a single value. The amount of radiation received in this study is within the dose guideline established by the NIH Radiation Safety Committee for research subjects. The guideline is an effective dose of 5 rem (or 5,000 mrem) received per year.

Table 1. Radiation associated with DEXA studies on forearm, spine, femur, and whole body.

Scans	**Millirems**
Anterior-posterior spine, DEXA	1.5
Anterior-posterior femur, DEXA	1.5
Total body scan, DXA	<0.05

The NIH Radiation Safety Branch monitors equipment and technique used in this study.

Age-associated strength loss (Grip Strength Test). Handgrip strength in both hands, measured using an adjustable, hand-held, hydraulic grip strength dynamometer, will be used as an overall assessment of physical strength and skeletal muscle function. Repeated measurement of grip strength over the follow-up visits will permit an estimate of strength loss over time. Grip strength is a commonly used indicator of health status and physical frailty and mid-life grip strength has been shown to be a strong predictor of early mortality.

The examination is done with the participant in the sitting position with the arm to be tested resting on the table and the elbow held at approximately a right angle. The dynamometer is held in the hand to be tested and is resting on a mouse pad. The participant is instructed to grip the two bars of the dynamometer in their hand, and to slowly squeeze the bars as hard as they can. The test is repeated on the other hand. This test is performed 3 times on each hand.

Exclusions. Participants who have had fusion, arthroplasty, tendon repair, synovectomy, or other related surgery of the upper extremity in the past 3 months will not be tested on the affected hand.

Risks. None are known.

Age-associated functional decline.

Sit-to-Stand Test. A commonly used performance-based test of physical function, the sit-to-stand test (also termed repeated chair stands), will be used to assess functional status at study inception and to tract loss of functional capacity over time. Using a standard armless chair placed securely against a wall, the participant is first instructed to rise from the chair without using arms and return to a seated position. If this is done successfully, the participant is then asked to repeat that movement 10 times. Performance, both whether 10 stands are completed and time to perform 5 or 10 stands has been strongly associated with onset of functional limitation, physical disability, institutionalization, and mortality.

Exclusions. There are no formal exclusions from attempting the single chair stand; inability to rise from a chair without using arms excludes participants from doing repeated chair stands.

Single Leg Stand Test. The single leg stand test should be performed with the participant standing a little less than an arm's length from a wall to provide an additional source of support if a loss of balance does occur. This test requires the participant to stand on one leg with the other leg flexed at the knee and held about two inches from the floor. The participant is asked to hold the position for as long as they can, up to 30 seconds. The single leg stand has been found to be a sensitive test of standing balance for middle age and older adults and has been used in numerous epidemiologic studies of well elderly without mishap.[45, 46]

Phase I – Screening, Recruitment and Household Interview

Protocol	Procedure	Where	Expected Time	Maximum Time
Screening	Identify eligible participant	Doorstep Interview	10 minutes	15 minutes
Recruitment	obtain IC for phase I	Home Visit	15 minutes	20 minutes
Demographics, Dental/Health Utilization, Stress, Neighborhood and Economic Survey	Household survey	Home Visit	55 minutes	65 minutes
Nutrition	Dietary Recall	Home Visit	20 minutes	30 minutes

Phase II – Medical Research Vehicle Examination

Protocol	Procedure	Where	Expected Time	Maximum Time
Enrollment	Obtain informed consent for phase 2	MRV II	20 minutes	25 minutes
Carotid & arterial stiffness	Carotid doppler ultrasonography, Pulse Wave Velocity, EKG	MRV I	40 minutes	50 minutes
Body Composition & Bone Mineral Density	Dual Energy x-ray absorptiometry (DEXA Scanner)	MRV I	30 minutes	35 minutes
Age-associated strength and function loss	Grip strength and lower extremity function test	MRV I	10 minutes	15 minutes
Overall health status	Blood Draw Buccal Mucosa Smear	MRV I	10 minutes	15 minutes
Overall health status & environmental exposure	Medical Hx & Physical Exam	MRV I	50 minutes	60 minutes
Nutrition	Dietary Recall	MRV I	20 minutes	30 minutes
Autonomic regulation	Ambulatory Monitoring	MRV II	45 minutes	55 minutes

Protocol	Procedure	Where	Expected Time	Maximum Time
	System			
Psychological Testing	Battery of cognitive functioning tests	MRV II	50 minutes	60 minutes
Mental Health & Income Screen	Audio-administered Questionnaire	MRV II	10 minutes	15 minutes

(b) Study Sample

The study plans to recruit a representative sample of whites and African Americans between 30 and 64 years old from twelve census tracts in Baltimore City in both low and high socioeconomic strata as a fixed cohort following the overall design. By collecting a baseline assessment and 5 follow-up triennial assessments over approximately 20 years, there will be sufficient power (>.80) with 30 participants per group (race by SES by sex by age group) remaining after 20 years. There will also be sufficient power (>.80) to compare rates of change among groups after the baseline assessment. Anticipating attrition due to non-response, morbidity, and mortality yields an initial sample of approximately 4,000 participants or about 335 participants per tract.

Inclusion Criteria:

- Age 30-64
- Able to give informed consent
- Able to perform at least 5 measures
- Must have valid picture identification

Exclusion Criteria:

- Pregnancy
- Within 6 months of active treatment of Cancer (Chemotherapy, biologic, radiation)

(c) Data Management

Data are kept in medical charts in locked file cabinets. All clinical research forms are filed in locked file cabinets. These materials are kept within a locked medical record room. Access to all study data is limited to HANDLS staff and investigators. Data are coded and entered by ID number only. Collaborators receive ID numbers only. No other identifying information is provided with the data.

(d) Data Analysis

The study employs a standard statistic software package depending on the independent and dependent variables being analyzed. Data analyses include logistic regression and mixed effects modeling.

(e) Facilities

All participant visits occur in the field. The first phase occurs in the participant's home and the second phase on the medical research vehicles. The vehicles have computer facilities for initial data entry. Computers located at the Gerontology Research Center and adjacent leased facilities provide additional computer support for data analysis and clean up. The clinical laboratory work will be done in the NIA Clinical Core Laboratory and at the Harbor Hospital Laboratory. Research lab values are run in CLIA approved intramural research program labs or sent out to private sector clinical laboratories.

(f) Project Organization

There are two MRV physicians, a nurse practitioner, ultrasonographer, cardiovascular technician, community coordinator, two security guards, vehicle drivers, vehicle logistician, psychometric tester, and psychophysiology tester. All HANDLS personnel report to the principal investigators as most are assigned to the Clinical Research Branch of the NIA IRP. The security guards, while specially trained for fieldwork on the vehicles, report to the head of security at the NIA IRP who is a member of the HANDLS logistics team. The Director of Security reports to the principal administrator of the NIA IRP and, therefore, to the Scientific Director and Deputy Scientific Director of the IRP. The principal investigators have been engaged in this research project for 5 years to date beginning with vehicle conception and design, support of the pre-pilot community-based research, development and implementation of the pilot, and ongoing development of the large planned population-based study.

(g) Project Schedule

September - November 2003	Complete pilot follow-up
October 2003- July 2004	Staff training for population-based study
August 2004	Begin field studies of census tracts in Baltimore City

Publications based on the follow-up data include:

- Muscle strength
- Premature osteopenia
- High rates of depressive symptomatology in men
- Utilization of the CES-D instrument in low SES urban, minority populations
- Recruitment and retention of an urban low SES African American populations

- The role of cultural competency training in clinical research among vulnerable populations

(h) Problems or Weaknesses

The weaknesses and potential problems of this study are similar to other longitudinal epidemiological studies, recruitment, and retention. Ideally, we would like to achieve a response rate of 85% for participation in both the household interview and the medical examination at testing at the mobile medical research vehicles. This rate may be unrealistically high. Anecdotal information from other ongoing epidemiological studies that have both interview and medical examination segments suggests a response rate of approximately 80% for the household survey and interview completion and a somewhat lower 60-75% completion rate for both the interview and the MRV examination and testing.

Risk/Benefit Assessment

There is very little risk to participants in this observational study. The exposure to low dose radiation from the analysis of bone density and body composition by the densitometer and the risks associated with having blood drawn are the only minimal risks.

The potential benefits to the participants include access to a full medical evaluation including screening for pathology in which early detection is advantageous. If the study doctor discovers any condition or problem, the information will be provided to the participant immediately and their primary care doctor, with their permission. If the participant does not have a physician, efforts will be made to refer them for care. Participants will be reimbursed for time and inconvenience.

The potential benefits to society relate to improvement of overall health in a vulnerable population that currently bears a disproportionate burden of disease and disability in this country. Healthy People 2010, the nation's disease prevention agenda, have defined two national goals to reduce preventable threats to the nation's health.[47] The first is to increase the quality and years of healthy life and the second is to eliminate health disparities. However, in order to achieve this second goal it is critical to develop research initiatives that provide new insights into the relationship between psychosocial factors and health status by (1) incorporating biological measures into large scale epidemiologic health and survey research projects and (2) the development and inclusion of a diverse panel of biomarkers or biologic measures that evaluate biologic pathways that may be involved in the causal relationship between SES and health.[48] This is what HANDLS attempts to accomplish. If successful, HANDLS will provide unique information that will hopefully uncover findings that will provide a basis for the development of appropriate prevention and intervention strategies to reduce health disparities.

Study Population – Gender and Ethnic Inclusion

In this study we will collect a representative sample of Baltimore City residents.

Recruitment Plan. The HANDLS study plans to recruit a representative sample of whites and African Americans between 30 and 64 years old from 12 census tracts in Baltimore City in both low and high socioeconomic strata as a fixed cohort following the overall design.

We are in negotiations to acquire the services of a Contractor to perform household listings, recruitment of a representative sample of African Americans and whites aged 30-64 from Baltimore City, and initial household interviews. The contract services provided by this procurement will supply us with expertise in contacting and recruiting a community-based representative sample that will comprise the foundation for our longitudinal study.

Work performed by the contractor shall proceed in two phases, household listings and participant recruitment. The Contractor shall perform this work in a 3-month dress rehearsal and in 12 3-month stands in pre-selected census tracts in Baltimore City.

Vertebrate Animals. None.

Consultants and Collaborating Agencies. Some staff positions in this study are filled through contracts with MedStar Research Institute, CODA and Westat. The Principal Investigators will provide technical supervision.

Curriculum Vitae and Biosketches. See attachments

Compliance. This trial will be conducted in compliance with this submitted protocol, U.S. Department of Health and Human Services, National Institutes of Health, Food and Drug Administration, ICH, and all applicable, state and local requirements.

Appendices

Household Survey
Audio-Administered Interview
Physical Exam Form
Medical History Form
USDA Multiple Steps for Dietary Recall
Cognitive Battery

Autonomic Regulation Materials

a. Instructions for Recall tasks
b. Anger Recall task (page 1) Happy Recall task (page 2)
c. Momentary mood scale

d. Houston Non-Exercise questionnaire (code for physical activity)
e. Subject run sheet

HANDLS Advertising Plan

a. Penny saver ad
b. Information booklet
c. Storyboard for videotape w/ dialogue

Informed Consent Document for Household and Nutritional Survey – Phase I
Informed Consent Document for Clinical Research (MRV) – Phase II
Informed Consent for Genetics Testing
Informed Consent Information Booklet
Authorization for HIPAA
Laboratory Panels

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