ASSOCIATION BETWEEN DIETARY SODIUM INTAKE AND BONE MINERAL DENSITY IN AN URBAN POPULATION OF AFRICAN AMERICANS

by

Jessica Rombach

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ABSTRACT

Osteoporosis is a public health concern due to the increasing number of adults over age 65 years, particularly among under screened urban, minority populations. High amounts of dietary sodium intake have been associated with a decrease in bone mineral density, but the results have been mixed, largely cross-sectional, and mostly examined in postmenopausal Caucasian women. The objective of this thesis was to examine the relationship between mean dietary sodium and calcium intakes and the change in bone mineral density from a sample of the Healthy Aging in Neighborhoods of Diversity Across the Life Span study prospective cohort between baseline (2004-2009) and wave 3 (first follow-up examination, 2009-2011) data collections. Nutrient intakes were estimated using two 24-hour dietary recalls collected using the Automated Multiple Pass Method, and bone mineral density was measured using duel energy x-ray absorptiometry at the total hip and lumbar spine. Data were analyzed using mixed models stratified by sex (SAS version 9.2). There was a significant inverse association between dietary sodium and bone mineral density of African American women at the hip site (-0.00002, P<0.05). However, the absolute bone density lost at the hip site of African American women between baseline and wave 3 (first follow-up examination) was not significant. Further research is needed using more than two data collection time points and a larger

sample of the cohort to enhance the modeling of dietary sodium intake and its effect on bone mineral density.

Chapter 1

INTRODUCTION

Osteoporosis and low bone mass, defined as having a bone mineral density Tscore (BMD) ≥ 2.5 and a T-score between 1.0 and 2.5 standard deviations below the average young adult, respectively, affects approximately 44 million US adults over the age of 50. Approximately 1.5 million of these adults will suffer an osteoporosis related fracture every year ¹. By 2030 the number of US adults aged 65 and older is projected to double to 71 million ². This sub-population increase makes osteoporosis prevention and treatment a priority.

Osteoporosis, low bone mass, and biomarkers of bone turnover are some of the top risk factors for future fragility fracture ³⁻⁶. Bone fractures lead to decreased mobility and quality of life, and a 2.8 to 4.0 times increased risk of mortality ¹. Bone health is the result of interactions between genetics, environment, and behaviors that all affect peak bone mass and subsequent bone loss ⁷. Nutrition, smoking, physical activity, medications and chronic alcohol consumption are modifiable behaviors that have significant impacts on bone loss ^{8, 9}. Dietary calcium and vitamin D are two nutrients widely recognized as having a significant direct impact on bone mass ^{4, 10, 11}. However, dietary sodium may also have a significant impact on bone health through its ability to increase renal calcium excretion by approximately 1 mmol for every 100 mmol of urinary sodium excreted ^{12,13}.

A 1961 animal study showed that during induced diuresis, urinary calcium excretion rates increased proportionately with increasing urinary sodium excretion rates. The proximal portion of the renal tubule reabsorbs 70% of filtered calcium parallel with sodium through passive paracellular transport, while only 8% of calcium reabsorption is actively regulated in the distal tubule ^{14,15}. This parallel transport can lead to a higher than normal loss of urinary calcium in the presence of an increased sodium load ¹⁶. Persistent loss of even 40 mg of urinary calcium per day can result in decreased serum calcium (<8.5 mg/dl), which then initiates an increase in parathyroid hormone (PTH). The cascade of compensatory mechanisms that follows PTH release includes an increase in bone turnover as evidenced by the appearance of specific biomarkers associated with bone loss and fracture risk ¹⁷.

The Healthy Aging in Neighborhoods of Diversity Across the Life Span (HANDLS) study is a cohort of roughly 3720 participants from an urban probability sample of 13 neighborhoods in Baltimore City, Maryland. Previous research in this cohort describes the sample as low fruit, vegetable, and dairy consumers with inadequate dietary calcium intakes ^{18, 19}. In addition, urban minority neighborhoods have been associated with health disparities and may be an under screened, at risk population for osteoporosis ²⁰⁻²². The existence of these dietary and healthcare patterns in the aging HANDLS cohort may increase the risk of bone loss due to increased dietary sodium consumption.

The primary objective of this study was to assess the relationship between mean dietary sodium and calcium intake and the change in BMD between baseline (2004-2009)

and wave 3 (first follow-up examination, 2009-2011) in a sample of the HANDLS study cohort. This study will also provide mean estimates of other nutrients important for bone health, specifically vitamin D, phosphorus, magnesium, potassium, and vitamin K, and bone density profiles of an under screened urban, minority population.

Chapter 2

LITERATURE REVIEW

This review focuses on dietary sodium intake and its relationship with changes in bone mineral density (BMD) and markers of bone turnover. The review is organized by first describing the research for the relationship between sodium and BMD and then sodium and biomarkers of bone turnover. Then the attenuating effects of dietary calcium are explored through the literature as well as other potential bone-related dietary nutrient confounders.

2.1 Sodium & Bone: Mechanism

A human case study in 1981 looked at the effects of high sodium loads through dietary methods rather than by infusion or diuresis, which was primarily used in animal studies. Six men ingested 400 mg/day of calcium in addition to varying dietary sodium loads (230 to 34,500 mg/day). The final increase in sodium intake caused a 22% increase in the filtered load of calcium and increased urinary calcium excretion to rates ranging from 59 mg/day to 262 mg/day ^{16, 23}. Multiple studies have shown that the transport of filtered sodium and calcium is consistently parallel in the proximal tubule under most conditions tested ²⁴⁻²⁶. Parallel transport is not the norm in the distal portion of the renal tubule, which complicates the relationship ²⁷. A controlled trial in rats found that certain medications might uncouple filtered sodium and calcium transport in the distal tubule ¹⁶. Other studies have imposed various conditions and found similar effects ^{28, 29}. It is clear

that these two ions have a significant relationship during filtration and reabsorption that is maintained in the proximal tubule during volume expansion, but not always in the distal tubule. Dietary sodium intake is seen as the director for both urinary calcium and sodium excretion ¹². The intricacy of this relationship and the complexity of the renal system make it difficult to precisely define the relationship between filtered sodium and calcium reabsorption, their excretion, and the subsequent serum calcium balance within the body.

Two systematic reviews explored the quantitative relationship between urinary sodium and calcium excretion. The first review found a median ratio of 0.69 mmol urinary calcium excreted for each 100 mmol increase in urinary sodium chloride excretion in healthy, non-kidney-stone-forming adults ³⁰. The second review found a similar 0.5 to 1.5 mmol (20-60 mg) increase in urinary calcium for every 100 mmol (2300 mg) of urinary sodium excreted ³¹. This relationship was independent of race ²³.

This finding could be translated to mean that a male who consumes 3762 mg of dietary sodium daily, would have a subsequent loss of 40 mg of urinary calcium above normal (assuming the Estimated Average Intake of 1500 mg/d for dietary sodium as normal). Urinary calcium loss coupled with a dietary intake of calcium below the Dietary Reference Intake (DRI) could exacerbate the relationship between an above recommended dietary sodium intake and increased bone turnover. Moreover, total body calcium imbalance and bone turnover may be accentuated in the aging and elderly populations that typically have decreased intestinal calcium absorption and faster than average rates of bone loss compared to young adults. The precise dietary sodium intake or threshold level that may cause an accelerated decrease in bone mass is not known.

The overall relationship between dietary sodium intake and bone health is depicted in **Figure 1**.



Figure 1: Effects of increasing dietary sodium chloride on urinary calcium excretion and bone metabolism in postmenopausal women ³².

2.2 Sodium & Bone Mineral Density

Bone is built and broken down over periods of time. Longitudinal data are required for an accurate illustration of dietary sodium's impact on the change in BMD, yet few studies have acquired such data. One longitudinal study found a significant association in a sample of Australian postmenopausal, white women (n-124) previously enrolled in a two-year calcium supplementation study. Participants completed weighedfood records, 24-hour urine samples, and had BMD measured at various sites using gold standard, duel-energy x-ray technology (DXA). Urinary sodium excretion was significantly correlated (r=-0.192, P<0.05) to the change in BMD at the total hip and intertrochanteric site. Significance remained after adjustment for age, weight, and activity confounders using multiple regression analysis ³³.

A recent 3-year longitudinal study examined this phenomenon using dietary sodium interventions. Healthy, postmenopausal Caucasian women (n=136, average age 63 years) were randomly assigned to a 1500 mg/d or 3000 mg/d sodium diet. Both groups received calcium and vitamin D supplements at adequate levels for their age. Participants recorded a 3-day food record and completed a 24-hour urine analysis every 3-6 months. DXA technology was used to measure BMD at various sites at each follow-up. Random effects regressions with repeated measures analysis of variance using cumulative data found significant main effects indicating that participants with higher urinary sodium had higher BMD measures in the forearm (t=2.63, p=0.0089) and in the spine (t=3.02, p=0.0027). This study found no detrimental effects on bone health at varying dietary sodium intakes when adequate calcium supplements were given ³⁴.

The other reviewed studies are cross-sectional and less indicative of the temporal relationship between dietary sodium and changes in BMD. A 1987 study of healthy postmenopausal women (n=440) assessed various metabolic and dietary variables in the urine and serum for a correlation with BMD. A significant negative correlation between

forearm BMD and 24-hour urinary sodium excretion was found ³⁵. A more recent crosssectional study in healthy young (n=102, average age 24 years) white women performed a regression analysis for hip BMD using activity, urinary sodium, and dietary calcium intake as dependent variables. Urinary sodium contributed to 5.9% (p=0.036) of the model's variation, but only in women with low calcium dietary intakes (<509 mg/1000kcal) ³⁶.

The only large sample (n=1098) to assess urinary sodium and BMD measures was in a population of elderly Chinese men and women. After the collection of a urine sample and bone scans at both the hip and lumbar spine, a logistic regression analysis found an inverse relationship between total hip BMD and urinary Na/Cr ratio ³⁷. Only one study design included African American postmenopausal women in addition to Caucasian women. These participants were assessed by food frequency questionnaire, 24-hour urine sample collections, and DXA. Linear regression analyses found that urinary sodium excretion in the range of 53.75 to 283.33 mmol/g/total volume, corresponding to dietary sodium intakes of 1236 to 6517 mg/day, was not associated with BMD of the hip while controlling for race ²³. Two additional cross-sectional studies in healthy older men and women found no significance between urinary sodium, measured by 24-hour urine collection, and BMD measured using DXA technology ^{38, 39}.

Currently there are only a few longitudinal studies that explore the relationship of dietary sodium intake and changes in BMD. This design seems to be the only logical way to analyze dietary sodium's effects on changes in BMD accurately, as changes in bone may not be detected over short periods of time. As a result, some of the contradictory findings mentioned above may be due to these inappropriate study designs. An increased appearance of biomarkers of bone turnover are a risk factor for fracture and are another measure of bone health that has been associated with dietary sodium intake and subsequent sodium excretion. These biomarkers are found in both the urine and the serum, are a less invasive measure, and are a better show the active bone resorption processes.

2.3 Sodium & Biomarkers of Bone Resorption

Markers of bone resorption, namely hydroxyproline, pyridinolines and deoxypyridinolines, NTx, CTx, and cross-linked telopeptide of type-1 collagen (ICTP) are valid indicators for risk of fracture and bone loss when BMD cannot be collected. An increased appearance of these biomarkers indicates an increase in the rate of bone resorption and thus may be used to assess the relationship between dietary sodium intake and changes in bone.

Urinary deoxypyridinoline showed a weak but significant correlation (r=0.32, p<0.0001) with 24-hour urinary sodium in Australian subjects (n=154) over a wide age range (20-72 y) ³⁸. A similar study methodology used in a population of elderly Japanese women found a significant positive relationship between urinary deoxypyridinoline and urinary sodium (r= 0.167, p<0.05) ⁴⁰. A population level health-survey analyzed hydroxyproline in young women compared to older women. The sodium/creatinine urinary excretion ratio was directly related to hydroxyproline/creatinine urainry excretion ratio in both age groups (r=0.341, p < 0.001) ⁴¹. Urinary sodium excretion may play a role in urinary calcium losses even at younger

ages, making low-sodium diets a plausible intervention for bone loss and subsequent low bone mass during aging.

Efforts to prevent increased bone turnover by limiting dietary sodium intake have been briefly studied. A randomized feeding trial of adults (age 23-76 years) found that eating the prudent DASH diet, which includes reducing dietary sodium intake and increasing intake of fruits and vegetables, reduced serum bone turnover markers osteocalcin (bone formation) and C-terminal telopeptide of type I collagen by 8–11% and 16-18% respectively (both p <0.001)⁴². Similarly, a clinical study examined salt restriction and bone turnover biomarkers. Fasting urine samples were obtained from postmenopausal women (n=59) before and after two to seven days of a dietary salt restriction. Urinary hydroxyproline was reduced in the urine after dietary restriction, but not significantly ^{43, 44}. These results indicate that both high and low sodium dietary intake have the potential to influence bone turnover rates.

The presence of increased biomarkers of bone resorption with decreased bone formation by osteoblasts results in more rapid bone loss over time. Despite these significant associations between dietary and/or urinary sodium and bone resorption biomarkers, it is unclear to what extent an increased appearance of these biomarkers in the serum and urine may have as an indicator for bone loss and changes in BMD over the periods of time observed in these studies.

2.4 Sodium & Bone: Calcium Dietary Intake

Calcium dietary intake and elevated intestinal absorption rates appear to attenuate the association between dietary sodium intake and appearance of increased biomarkers of

bone resorption, and possibly the association with BMD measures. Higher levels of dietary calcium intake and/or intestinal absorption rates compensate for urinary calcium losses and aid in normalizing serum calcium levels, thus reducing the impact of dietary sodium-induced calciuria.

Typical rates of intestinal calcium absorption are low, estimated to be between 10 to 30%. A controlled trial in 11 patients put on a high sodium diet found that induced hypercalciuria significantly increased fractional intestinal calcium absorption (0.39 to 0.49, p<0.05)⁴⁵. This increase in absorption provides a protective effect during a period of increased urinary calcium excretion and, depending on the usual dietary calcium intake of the individual, may be enough to offset losses from dietary sodium-induced hypercalciuria.

Postmenopausal women may have a diminished ability to increase intestinal absorption. Thus a stronger association between dietary sodium intake and markers of bone resorption may exist. A low calcium diet in addition to decreased intestinal absorption may further strengthen the association between dietary sodium and changes in BMD. A previously mentioned study in a population of postmenopausal African American and Caucasian women found that lower intakes of dietary calcium (\leq 1000 mg/day) made participants significantly (p<0.01) more susceptible to calciuria. A regression analysis of urinary sodium excretion on calcium excretion was significant only at the lower intakes of dietary calcium (coefficient=0.012, p<0.01)²³. Despite these results, it is unknown if low dietary calcium intakes affect other age groups or males in a similar fashion.

An experimental comparison study put healthy post and premenopausal women on a high sodium diet (6,900 mg/d) and then on a low sodium diet (1,150 mg/d) for a week each. At the end of each week, blood and urine samples were collected to determine bone turnover. Only postmenopausal women had a significant increase (27%, P.0.024) in urinary deoxypyridinoline/creatinine when crossing over from the lowsodium diet to the high-sodium diet ⁴⁶. However, dietary calcium was not measured or controlled in this study.

A cross-sectional analysis of healthy pre-menopausal women attempted to shed light on the importance of dietary calcium for the relationship between dietary sodium and changes in BMD. The recruited participants completed a validated diet history questionnaire and had BMD measured using DXA at various sites. Participants' calcium intakes were adjusted relative to total energy intake and categorized as high or low (\leq or> 506 mg/1000 kcal/day). Pearson correlations between BMD at the total hip and urinary sodium excretion were only significant in the lower calcium consuming group (r=-0.36, p=0.009)³⁶. This study not only alluded to dietary calcium's potential protective role against urinary calcium loss and bone loss, but also that dietary calcium intake may be important at both younger and older ages.

These studies provide enough evidence for a moderately strong attenuating effect of dietary calcium for the relationship between dietary sodium intake and changes in BMD. For the purposes of this thesis dietary calcium intake will always be considered when assessing the relationship between sodium and bone health.

2.5 Other Potential Dietary Confounders

A recent review of the literature on dietary sodium and BMD highlighted a large number of confounding variables inherent in most dietary studies that are often overlooked ⁴⁷. A number of factors are well known to be associated with osteoporosis risk such as smoking, chronic alcohol consumption, high and low body weight, low physical activity and strength, hormone imbalances, and several medications ¹.

Other confounders not controlled for in previous dietary studies arise from the tendency to focus analyses on single nutrient effects. It has been suggested that accounting for multiple nutrients or meal patterns as covariates may better describe the risk of chronic disease from a single nutrient ⁴⁸. Specifically for osteoporosis the important nutrients to include in analyses as confounders are: potassium, magnesium, vitamin D, vitamin K and phosphorus.

Potassium intake (60 mmol/d of ingested KHCO3 decreases urinary calcium excretion by 0.9 mmol/d^{13,49}) may affect calcium reabsorption in the renal tubules^{23,50-53}. Phosphorus and magnesium reabsorption are both independent of calcium reabsorption in the renal system, but their consumption does have a significant effect on calcium balance and bone mineralization^{54,55}. Proper bone formation may even be stunted if the ratio of calcium to phosphorus is too high in the diet (>1.6:1)⁵⁶. Vitamin D is known to enhance calcium absorption in the small intestine and is also a component of calbindin carrier protein in the renal system and aids in the reabsorption of filtered calcium during fluid expansion. And finally, poor vitamin K status assessed using low serum levels, low intake, and elevated Gla-protein osteocalcin, was associated with low bone mass, osteoporosis and fracture risk ⁵⁷.

2.6 Summary

Osteoporosis is a serious condition resulting in decreased quality of life and increased mortality risk. The prevalence of osteoporosis is projected to increase as our population ages. Dietary sodium has been shown to potentially influence urinary calcium excretion and cause subsequent elevated bone resorption. Prolonged bone resorption processes occurring without accompanying bone formation can lead to diminished bone mineral density over time. Low socio-economic and aging populations are likely to be more at risk for these effects due to higher sodium-containing food patterns and low intakes of bone-related dietary nutrients.

The reviewed literature lacks statistically large, prospective studies in populations habitually consuming sodium above 2300 mg/day; the recommended level of dietary sodium for roughly 50% of healthy adults according to the 2010 Dietary Guidelines for Americans and the Institute of Medicine (IOM) ^{58, 59}. Only a single observational, longitudinal study showed significant results for the relationship between dietary sodium intake and BMD ³³. However, multiple significant associations between urinary sodium and bone resorption biomarkers have been found ^{38, 41, 60}. This finding reinforces dietary sodium's role in bone health. Past studies have been of short duration, small sample size, or were interventions with atypical dietary sodium intakes and adequate calcium dietary intakes.

The measurements of bone heath outcomes in most studies have not been BMD but rather bone resorption biomarkers. Studies have focused on total body calcium balance and bone turnover using short-term dietary sodium interventions or crosssectional designs. The assessment of changes in BMD needs to be over time as bone is slowly built and broken down during the aging process. There is biologic plausibility that higher than recommended dietary sodium intake may increase bone resorption with minimal bone formation and eventually decrease BMD over time. No human studies have longitudinally observed usual dietary intakes of high sodium (>2300 mg/day), lowcalcium (<800-1000 mg/day) patterns and the relationship with BMD in order to observe growth trends. Furthermore, no research of this kind exists in an urban population of mixed race and socioeconomic statuses.

2.7 Research Aims

2.7.1 Is there an association between mean dietary sodium intake and bone mineral density at the lumbar spine or at the total hip between baseline (2004-2009) and wave 3 (first-follow-up examination (2009-2011) among a sub-sample of the HANDLS study cohort.

We hypothesize that mean dietary sodium intake will have a significant inverse relationship with bone mineral density changes at both bone sites over the data collection time period.

2.7.2 Does consuming the recommended amount of dietary calcium protect against changes in bone mineral density that may occur while consuming higher intakes of dietary sodium.

We hypothesize that bone mineral density will only be significantly related with dietary sodium intake if the mean dietary calcium intake is below the recommended levels set by the Dietary Reference Intakes.

2.7.3 Describe the HANDLS cohort sample's absolute bone mineral density, Z and T-scores, and evaluate the adequacy of bone-related dietary nutrient intakes compared to the Estimated Average Requirements and Adequate Intakes.

We hypothesize that the urban HANDLS cohort sample will have lower bone mass compared to national averages and will have a low percentage of the sample with adequate intakes of bone-related dietary nutrients.

Chapter 3

METHODS

3.1 Study Background

The HANDLS study is a multidisciplinary, prospective epidemiologic cohort study examining the independent influence and interaction of race and socioeconomic status (SES) on the development of cardiovascular and cerebrovascular health disparities among African American and White populations. This study was designed as a 20-year study with at least three follow-up waves.

The participants were screened from 13 neighborhoods and were chosen to accommodate the 4-way factorial cross design of the study, which includes individuals from both below and above 125 % of the poverty level, both males and females, both African Americans and whites, and individuals aged 30 to 64 years. Inclusion criteria for the study were the ability to give informed consent, aged 30-64 years, a valid picture identification, and the ability to perform at least five of the following evaluations: medical history, physical performance, cognitive testing, dietary recall, audio questionnaire, body composition, carotid Doppler, or pulse wave velocity assessment. Individuals with Acquired Immunodeficiency Syndrome (AIDS), pregnant women and individuals within six months of cancer treatment were excluded from the study. All participants were provided a written informed consent (See APPENDIX E) and were

compensated for their participation in addition to the inherent benefits of expense-free medical testing and screening.

3.2 Baseline Study Protocol

Baseline data collection began in August 2004 and was completed in March 2009. Baseline data collection was done in two phases. The first phase included in-home questionnaires on health status, psychosocial factors, neighborhood characteristics, demographics, and a 24-hour dietary recall. The second phase was scheduled for approximately seven to ten days later when participants visited the mobile research vehicles (MRVs). The MRV was where a physical exam, medical history, second 24hour dietary recall, psychophysiology assessments, laboratory measurements, DXA scans, and a cognitive evaluation were collected for all participants. This study protocol was approved by both of the human subjects review boards at Medstar Health Research Institute and the University of Delaware.

Midway through baseline collection, an interim contact study known as wave 2 was implemented. The purpose of the wave 2 study was to collect personality and coping data on a subset of the cohort and to maintain contact with participants in hopes of combating high transiency rates among urban low SES populations who are known to move frequently resulting in high rates of study attrition. This interim study explains the larger than expected gap in between baseline and wave 3 (first follow-up examination) time points.

3.3 Wave 3 (First Follow-up Examination) Study Protocol

The same HANDLS cohort was revisited from July 2009 to July 2013. The same exclusion and inclusion criteria applied at the wave 3 (first follow-up examination) data collection with the exception of age and AIDS status. A written consent was again obtained (APPENDIX F). Participants were ineligible to participate in wave 3 (first follow-up examination) if they were currently pregnant or physically unreachable (i.e. jail or prison). The study protocol for the wave 3 (first follow-up examination) was nearly identical to baseline study protocol with a few efficiency improvements and added measures such as performance testing.

Wave 3 (first follow-up examination) data were collected in phases. The first phase was done on the MRV lasting about four hours and 25 minutes and included: an interim medical history and physical examination, 24-hour dietary recall, cognitive evaluation, echocardiography, assessments of muscle strength and bone density, laboratory measurements, and an audio-administered questionnaire. The second phase of data collection was done via telephone survey approximately 7-10 days later, which included a second 24-hour dietary recall and supplement questionnaire that took roughly 30 minutes to complete. This study protocol was also approved by both of the human subjects review boards at Medstar Research Institute and the University of Delaware.

3.4 Participants

This thesis analyzes a subset of the sample population from baseline data collection (August 2004-March 2009) and matching participants from wave 3 (first follow-up examination, July 2009–February 2011). Wave 3 (first follow-up

examination) participant nutritional data from March 2011 to June 2013 were not compiled in time for this thesis. Recruitment of the HANDLS cohort has been described previously in a publication by Evans et al ⁵⁸. **Figure 2** shows the details of the baseline accrual.



Figure 2. HANDLS baseline accrual four-way factorial design.

The baseline HANDLS study population consisted of a cohort of 3,720 African American and white adults from an area probability sample of Baltimore City, Maryland ⁵⁹. Of the 3720 participants from baseline (2004-2009), 2,802 were examined on the mobile research vehicles (Figure 3). As of February 2012 when the data for this thesis began only 308 participants had completed two dietary recalls and DXA scans for the total hip and lumbar spine at both baseline and wave 3 (first follow-up examination).

Of the 308 eligible participants 152 participants were excluded due to chronic alcohol use (defined as >150 g/day at both time points) or due to use of medications that impact bone and all 78 white participants were excluded ^{9, 61} (See APPENDIX C for full list). Due to the MRV neighborhood visitation schedule for wave 3 (first follow-up examination) the number of white participants compiled in this sample at the time of this analysis was too low to have power for significance tests. Therefore, the final participant sample came to total of 156 African American participants as detailed in **Figure 3**.



Figure 3: Flow of HANDLS participant sample inclusions and exclusions.

3.5 Description of Relevant Procedures From Baseline and Wave 3 (first follow-

up examination)

The following relevant procedures were performed for both the baseline and wave

3 (first follow-up examination) data collection time points unless otherwise noted:

3.5.1 Household Survey (Baseline only)

The household survey was performed by a trained interviewer in the participant's home and gathered 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.

3.5.2 Medical History and Physical Examination

A physician and/or nurse performed a comprehensive physical examination and medical history with each participant on the MRV. The purpose of the physical examination and medical history was to document diagnosable conditions, measure anthropometrics, to record medications, frequencies and dosages, and to assess disabilities that might limit independent functional activities. This examination provided data on height, weight, smoking status, and medications that may affect bone density.

All anthropometric measurements of participants were recorded and collected as data either by the cardiac technician, physician, or nurse. The resultant data were entered and stored electronically. Weight was measured with a Health O Meter Digital Lithium Scale (Model #HDL 976) that was calibrated monthly. Weight measurements were obtained on participants in the morning when they arrived at the MRV 1 prior to breakfast. Participants were required to remove their coats and any object that could bias the accuracy of their weight measurement. To activate the scale, the technician stepped on and off the platform to test if the scale was properly activated and displayed a zero. Then a participant was instructed to step on the scale and stand precisely in the middle of the weighing platform looking straight ahead without moving. The stable weight reading was recorded to the nearest one-tenth in pounds, then converted to kilogram scale by dividing by 2.2 and recorded on the Electronic Data Entry Form (EDEF). The maximum measurable weight for this scale is 350 lbs. Participants who estimated their weight as greater than 350 lbs. were verified by having the participant step on the scale. If scale reports error message, then participant's estimated weight was used.

Height was measured using a Novel Products Inc. Height Meter (Model #DES 290237). Participants were instructed to take off their shoes and put on a pair of booties that was provided for them before height was taken. To ensure an accurate standing height measurement, participants were encouraged to stand erect on the floor with heels placed together and touching the wall behind them and backs against a vertical height meter mounted securely on the wall. Participants were required to maintain this erect posture looking straight ahead without tilting their head up or down. The technician ensured that a participant was correctly positioned before sliding the lever on the height meter down until the lever came to rest horizontally on a participant's head. If participants were taller than the technician, the technician used the nearby footstool to facilitate an accurate measurement. The height was recorded at the level of the Frankfort horizontal plane as the nearest centimeter corresponding to the lowest point on the lever. Height measurements were obtained and recorded to the nearest centimeter by rounding up to the nearest whole number.

Medication information was collected on the MRV by an examiner (nurse, nurse practitioner, physician, ultrasound technician, or cardiology technician). Medications were recorded on an electronic tablet or laptop computer within the HANDLS medical history program. This computerized program was dynamic: it was continually updated and refined for common usage, trade names, generic equivalents and commonly used dosages. The NDC codes from the Food and Drug Administration (FDA) were used and served as a drop down window in the computerized program. The examiner recorded the name, strength, dosage, start date and reason for medication usage.

3.5.3 Dietary Recall

Participants were asked to recall all of the foods and beverages they consumed during the previous 24 hours. A trained interviewer recorded the dietary recall using methods developed by the USDA called the Automated Multiple Pass Method (AMPM). Versions 2.3-2.5 were used for baseline and for wave 3 (first follow-up examination). The AMPM program is supplemented by measurement aids and illustrations to assist in estimating accurate quantities consumed. The validity of the AMPM was established in a study using doubly labeled water ^{62, 63}.

The dietary recalls were coded using Survey Net, matching the foods consumed with codes in the Food and Nutrient Database for Dietary Studies version 3.0 for baseline data and version 5.0 for the wave 3 (first follow-up examination) ⁶⁴. This procedure provided data to determine the mean intake of dietary sodium, calcium, energy, potassium, vitamin K, phosphorus, vitamin D, magnesium and alcohol intake. Dietary sodium intake was not adjusted for salt added at the table, however, USDA recipes for prepared dishes automatically included salt added in preparation. There were no upper or lower limits on nutrient intakes, however the coded food data were run through multiple quality control checks to assure that there were no errors in coding and that data from fasting or unreliable participants were flagged and assessed for validity and inclusion by trained food coders. At the nutrient analysis level, nutrient outliers are subject to quality. Dietary recall data flagged as unreliable or that did not pass quality control checks were not included in further analyses.

3.5.4 Bone Density and Body Composition

Dual energy X-ray absorptiometry (DXA) was performed for the total body, the lumbar spine, and the total hip using a Lunar DPX-IQ (Lunar Corp., Madison, WI) at baseline data collection and a Discovery QDR series (Hologic, Bedford MA) at the wave 3 (first follow-up examination) data collection. An unpublished comparability study was previously conducted on a small sample of the HANDLS participants using Bland-Altman statistics for cross-calibration between the Lunar and Hologic machines and showed a strong correspondence between the two devices ⁶⁵.

The DXA measurements were taken and read by one of two physicians at baseline and by a different single physician at wave 3 (first follow-up examination). DXA delivers a small amount of radiation through an X-ray source in a scanning arm while the participant was supine or seated. A quality assurance (QA) test was run daily before performing any bone scans. The QA test verifies the correct operation of the densitometer as well as functionality, accuracy and precision of the densitometer. The QA took approximately 15 minutes to complete with less than one minute of operator intervention involved. In addition, a spine phantom measurement was run daily. The spine phantom mimicked the typical size and density range of a normal human spine consisting of the L1 through L4 vertebrae with ½ of T12 and L5 as landmarks for correct positioning. Sitespecific scans of the lumbar spine and right hip provided information on the bone area (cm²) and bone mineral density (g/cm²). Total body scan measured body composition in terms of bone mineral content (g), bone area (cm²), bone mineral density (g/cm²), 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 were taken for the body as a whole as well as for the arms, legs, trunk, head, pelvis, and spine. Complete instructions for the site-specific measurements and total body scan are in APPENDIX D.

Prior to the scan, participants were instructed to remove any attenuating material including clothing with metal or plastic, jewelry, shoes, brassieres, belts or glasses. The participant then sat upright on the center of the table so that the centerline ran through the center of the pelvis and so that the spine was lined up the centerline. Then the participant was told to lie on their back and had the thickness of their stomach area measured using calipers and the correct mode was chosen based on desired screen site.

DXA Z and T-scores were interpreted by a single medical physician at wave 3 (first follow-up examination). Standard deviation Z and T-scores were automatically produced from the Hologic machine based on the Hologic reference database matched for age, gender, and race when appropriate. This machine calculates a Z or T score for each participant, which is then categorized into a Z or T score category depending on age. Participants received a Z or T-score depending on whether they were 50 years of age and younger (Z-scores) or older than 50 years of age (T-scores). Participants' Z-scores aged 50 years and younger could only have been categorized into a Z-score category of 0 or 4. Category 0 indicated that BMD was within expected for age. Participants' T-scores above the age of 50 could have been categorized into categories 0,1, or 2. Category 0 indicated a BMD within expected range for age, category 1 indicated the presence of low bone mass, and category 2 indicated the presence of osteoprorsis.
The DXA measurements were not administered to individuals who have had both hips replaced or to individuals weighing greater than 300 pounds at baseline (Lunar) and 450 pounds at first follow-up (Hologic) due to the densitometers' limitations.

3.5.5 Sit-to-Stand Test/Repeated Chair Stand (Age-associated functional decline; wave 3, first follow-up examination only)

A commonly used performance-based test of physical function, the sit-to-stand test (also termed as repeated chair stands), was used to assess functional status and lower extremity strength and to track loss of functional capacity over time 66 .

A trained examiner conducted these tests with each participant. The procedure was first explained and performed by the examiner so that the participant understood the task. Then using a standard armless chair placed securely against a wall the participant was first instructed to rise completely from the chair without using his or her arms and then return to a seated position. If this was done successfully, the participant was then asked to repeat that movement 10 times as quickly as possible without stopping while keeping his or her arms folded across the chest. Participants were told to make sure they rose completely each time. There were no formal exclusions from attempting the repeated chair stand except for inability to rise from a chair without using arms.

3.6 Statistical Analysis

Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). First, frequencies were generated for select household and medical survey characteristics. Next, means \pm standard errors were computed for select dietary bone-related nutrients (sodium, calcium, vitamin D, energy, potassium, magnesium,

phosphorus, and vitamin K), BMD and body fat percentage at both baseline and wave 3 (first examination follow-up). Then, the percentage of the participant sample that fell below the estimated average requirement (EAR) or adequate intake (AI) for the selected bone-related nutrients was calculated (exception being sodium calculated as percent above AI). Paired t-tests and McNemar's tests for paired samples were used to test for differences between means and frequencies between baseline and wave 3 (first follow-up examination) with a level of significance set to p < 0.05.

In addition, the percentages of the participant sample falling within age-matched Z-score categories (0 through 4) were calculated based on DXA output at wave 3 only (first examination follow-up). Lastly, unconditional means models were used to find covariates by sex that fit the model of dietary sodium and calcium intakes' effect on bone density. The Akaike information criterion was used as a measure of the relative quality of the statistical model for this data set. Mixed models using repeated measures with random intercepts stratified by sex were generated to show the effects of dietary sodium and calcium intake on bone density at the total hip and lumbar spine sites adjusted for smoking, age, body fat percentage, poverty status, and potassium.

Chapter 4

RESULTS

Descriptive statistics for this sample (N=156) of the HANDLS cohort is presented in Table 1. There were 80 African American men and 76 African American women. The mean time elapsed between baseline and wave 3 (first follow-up examination) was $4.8 \pm$ 0.1 years for both African American women (AAW) and African American men (AAW). Approximately 1 in 3 African Americans were below 125% of the 2003 federal poverty level based on yearly total family income and household number ⁶⁷. Over half of the sample had at least a high school/GED level education, but only 1 in 12 had a college equivalent or greater (**Table 1**). Table 1: Characteristics of the African American women (AAW) and African American men (AAM) in the HANDLS cohort sample who participated in baseline data collection (2004-2009))*

Characteristic	AAW (n=76)	AAM (n=80)
Age $(X \pm SE)$	46.8 ± 1.1	47.3 ± 1.0
SES <125% of federal poverty level** (%)	32.7	30.8
Education (%)		
< High school	31.6	37.9
High school/GED	27.6	37.5
> High school < College degree	32.9	18.8
\geq College degree	7.9	6.3
Chronic Smokers*** (%)	42	63

* Includes only those subjects with DXA measures and two dietary recalls at baseline and wave 3 (first follow-up examination) HANDLS study.

** Income guidelines based on the 2003 Federal Poverty Income Guidelines ⁶⁷. ***Chronic smokers defined as participants who smoked at both baseline and wave 3 (first follow-up examination).

Between baseline and wave 3 (first follow-up examination) there were significant changes in BMD at both the lumbar spine and hip sites for AAM only (Table 2). A significant change in BMD among AAM was observed at the lumbar spine (0.5 % per year) and total hip (0.4 % per year). Both men and women saw a significant decrease in percent body fat based on DXA measures of body fat between baseline and wave 3 (first follow-up examination). AAW women also saw a significant decrease in the percentage of women considered obese. The percentage of men and women who completed the chair stand test improved between baseline and wave 3 (first follow-up examination), but was not significant.

Table 2: Comparison of absolute bone mineral density (BMD), body composition, and sit to stand test in the HANDLS cohort sample of African American women and men (AAW/AAM) at baseline (2004-2009) and wave 3 (first follow-up examination, 2009-2011)****

		AAW (n=76)		AAM (n=80)		
	2004-2009	2009-2011	p value*	2004-2009	2009-2011	p value*
Bone Mineral Density (X±SE)						
Lumbar Spine (g/cm ²)	1.14 ± 0.02	1.13 ± 0.02	0.559	1.16 ± 0.01	1.13 ± 0.02	0.0046
Total Hip (g/cm ²)	1.08 ± 0.02	1.09 ± 0.02	0.5641	1.11 ± 0.02	1.09 ± 0.01	0.0012
Body Composition						
Percent Body Fat (X±SE)	42	36.2	< 0.0001	22.7	20.7	0.0009
Obese DXA** (%)	75	57.9	0.0029	0	0	NA
Sit to Stand Test	64/	69/		70/	74/	
(%/seconds <u>+</u> SE)***	38.0 ± 1.6	35.3 ± 1.0	.115	33.5 ± 1.0	32.7 ± 0.8	.354

*P-values from paired t-test; level of significance p <0.05

*** Defined as DXA >25% men, >35% women by AACE/ACE Task Force ***Sit to Stand Test: Measures age-associated muscle performance and decline. Presented as completion of 10 stands [%] and mean time to complete 10 stand [s]) **** Includes only those subjects with DXA measures and two dietary recalls at baseline and wave 3 (first follow-up examination) HANDLS study. Mean age of men and women at baseline were 47.3 ± 1.0 and 46.8 ± 1.1 years old,

respectively, with an average increase of 4.8 ± 0.1 years at wave3 (first follow-up examination).

BMD Z and T-scores were based on the clinical diagnosis at the right hip or spine sites for wave 3 (first follow-up examination) only using the Hologic DXA instrument and are presented in Tables 3a and 3b. Almost all (97%) of the AAW aged 30-50 had BMDs that were within normal range for expected age. However, 27.9% of AAW aged 51-64 at wave 3 (first follow-up examination) were categorized as having low bone mass, and 23.3 % as having osteoporosis. The Z and T-scores for men had a different pattern. Unlike the AAW, more of the AAM aged 30-50 had BMDs below the normal range expected for age (3% versus 21.9%, respectively). An estimated 56.3 % of AAM aged

51-60 at wave 3 (first follow-up examination) had low bone mass, and 18.8% had

osteoporosis.

Table 3a: Bone mineral density (BMD) Z-score categories for the hip or spine site for the HANDLS cohort sample of African American women and men aged 30-50 years old (AAW/AAM) at wave 3 only (first follow-up examination) (2009-2011)**

	2009-2011		
BMD Z-score Category*	AAW (n=33)	AAM (n=32)	
	Ages 30-50	Ages 30-50	
0 (%)	97	78.1	
4 (%)	3	21.9	

*Z-score: Determined by clinical diagnosis of the lower value at the right hip and spine sites at the wave 3 (first follow-up examination) using the Hologic DXA machine. Participants' Z-scores who are 50 years old and younger may either be categorized with a 0 (within range/normal) or a 4 (below range for expected age).

**Mean ages of men and women at baseline were 43.5 ± 0.7 and 42.8 ± 0.8 years old, respectively, with an average increase of 4.8 years at first follow-up examination.

Table 3b: Bone mineral density (BMD) T-score categories for the hip or spine site for the HANDLS cohort sample of African American women and men aged 51 years and older (AAW/AAM) at wave 3 only (first follow-up examination) (2009-2011)**

	2009-2011			
BMD T-score Category*	AAW (n=43)	AAM (n=48)		
	Ages 51-64	Ages 51 and older		
0 (%)	48.8	25		
1 (%)	27.9	56.3		
2 (%)	23.3	18.8		

*T-score: Determined by clinical diagnosis of the lower value at the right hip and spine sites at the wave 3 (first follow-up examination) using the Hologic DXA machine. Participants' T-scores who are 51 years and older may be categorized as a 0 (within normal range), 1 (low bone mass) or 2 (osteoporosis).

**Mean ages of men and women at baseline were 58.3 ± 0.8 and 57.7 ± 0.7 years old, respectively, with an average increase of 4.8 years at first follow-up examination

There were no significant changes in reported intake of key bone-related dietary nutrients, namely sodium, calcium, magnesium, vitamin D, phosphorus, potassium, and vitamin K, between baseline and wave 3 (first follow-up examination) (Table 4). At first follow-up examination, mean dietary sodium intake was 2875 mg/day and 4144 mg/day for AAW and AAM, respectively. At first follow-up, mean dietary calcium intake was 688 mg/day and 944 mg/day for AAW and AAM, respectively.

Table 4: Comparison of select bone-related mean dietary nutrients intakes of the HANDLS cohort sample of African American women and men (AAW/AAM) between baseline (2004-2009) and wave 3 (first follow-up examination, 2009-2011)**

Energy and Nutrient Intake	AAW (n=76)			A	AM (n=80)	
	X <u>+</u> SE				X <u>+</u> SE	
	2004-2009	2009-2011	p value*	2004-2009	2009-2011	p value*
Energy (kcal)	1855 ± 103	1752 ± 79	0.26	2613 ± 147	2505 ± 135	0.4643
Sodium (mg)	2818 ± 166	2875 ± 128	0.7112	3955 ± 135	4144 ± 232	0.4572
Calcium (mg)	637 ± 43	688 ± 49	0.2975	832 ± 55	944 ± 60	0.089
Vitamin D (mcg)	3.0 ± 0.3	3.0 ± 0.3	0.454	4.6 ± 0.4	5.3 ± 0.5	0.2315
Phosphorus (mg)	1060 ± 62	1020 ± 52	0.488	1471 ± 83	1448 ± 81	0.8068
Magnesium (mg)	216 ± 12	220 ± 11	0.7449	290 ± 18	284 ± 13	0.7514
Potassium (mg)	1972 ± 128	1989 ± 100	0.8874	2721 ± 156	2616 ± 127	0.4819
Vitamin K (mcg)	129 ± 21	118 ± 21	0.7151	137 ± 25	106 ± 11	0.2477

*P-values from paired t-test; level of significance p <0.05.

** Includes only those subjects with DXA measures and two dietary recalls at baseline and wave 3 (first follow-up examination) HANDLS study.

The overall diet of the HANDLS sample appears inadequate, as the majority of the sample does not meet the estimated average requirements (EAR) for the nutrients thought to enhance bone health (calcium, vitamin D, and magnesium), with the exception of phosphorus (Table 5). Further, the majority of this sample also fails to meet the adequate intakes (AI) for both vitamin K and potassium. The percent of the sample with mean intakes less than the EAR for calcium was the only striking difference between men and women. Only 1 in 5 women in this sample received greater than or equal to the EAR for calcium compared to about half of the men. Almost all of the participants exceeded the daily AI for dietary sodium. There were no significant changes between baseline and wave 3 (first follow-up examination) in the percentage of participants meeting or

exceeding the EAR's or AI's for these nutrients.

Table 5: Comparison of the frequency of the HANDLS cohort sample of African American women and men (AAW/AAM) that do not meet the estimated average requirement (EAR) or adequate intakes (AI) for selected bone-related dietary nutrients at baseline (2004-2009) and wave 3 (first follow-up examination, 2009-2011)***

Nutrient		AAW (n=76)			AAM (n=80)	
	%	less than EAR ³	*	9/	6 less than EAR	
	2004-2009	2009-2011	p value**	2004-2009	2009-2011	p value**
Calcium (mg)	80	79	0.8084	55	45	0.1701
Vitamin D (mcg)	99	96	0.3173	91	90	0.763
Magnesium (mg)	76	68	0.2008	79	79	1
Phosphorus (mg)	9	15	0.3173	5	4	0.7055
	Q	% less than AI			% less than AI	
Potassium (mg)	97	100	N/A	91	95	0.3173
Vitamin K (mcg)	62	61	0.8575	73	73	1
	%	greater than AI	*	%	greater than AI	· · · · · · · · · · · · · · · · · · ·
Sodium (mg)	90	90	1	93	95	0.5271

* Dietary Reference Intake values listed in APPENDIX A

**McNemar's test for paired samples; p<0.05 significant.

*** Includes only those subjects with DXA measures and two dietary recalls at baseline and wave 3 (first follow-up examination) HANDLS study.

To examine the relationship between diet and bone outcomes, general linear

mixed models for total hip and lumbar spine BMD for the sample were stratified by sex examining the main effects dietary sodium and calcium, as well as other covariates and factors important to the model (Table 6). The models indicate that age has a significant direct association with BMD for AAM and AAW at the lumbar spine. Age was only significant for AAM at the hip site. AAW smokers had a significant inverse effect on BMD at the hip (β = -0.1026) and the lumbar spine (β = -0.0811). Body fat percent had a significant predictive relationship with the lumbar spine BMD for both sexes, but it was not a significant for hip BMD.

Mean dietary calcium and sodium did not show consistent significant effects across bone sites and sex, and were not significant predictors of BMD for either bone site among the AAM in this sample. Mean dietary sodium intake had an inverse relationship with BMD only at the AAW hip site. Dietary calcium only had a significant relationship with BMD of the lumbar spine site among the AAW.

The only bone-related dietary nutrient covariate included in the final model was potassium, however it was not a significant effect on BMD at either site. Energy was excluded from the model due to a collinear effect on BMD with potassium. Education and the sit-to-stand test did not contribute to the goodness of fit for this model and therefore not included in the final model. Table 6: General linear mixed model with repeated measures for lumbar spine and total hip bone mineral density (BMD) as a function of mean dietary sodium and calcium intake of the African American women (AAW) and African American men (AAM) in the HANDLS cohort sample**

	SPINE BMD		HIP BMD	
	AAW (n=76)	AAM (n=80)	AAW (n=76)	AAM (n=80)
Variable	ß estimate	ß estimate	ß estimate	ß estimate
Intercept	1.1234	1.1838	1.222	1.3126
Age	-0.00351*	-0.00365*	-0.00162	-0.00409*
Povstat (below)***	-0.04225	0.04556	-0.07145	0.03369
Smoker (non- smoker)****	-0.0811*	0.02837	-0.1026*	-0.01623
Sodium	-0.0002	-0.000008	-0.00002*	-0.000004
Calcium	0.000074*	0.00004	-0.00002	-0.00001
Potassium	0.000015	0.000012	0.000017	0.000007
Body fat percent	0.005001*	0.003486*	0.001018	-0.00009

Unconditional means model were used to find predictors using optimal AIC method. The mixed models with repeated measures and random intercept is shown.

*Significant p < 0.05

** Includes only those subjects with DXA measures and two dietary recalls at baseline and wave 3 (first follow-up examination) HANDLS study.

*** Below the 125% of the poverty level based on the 2003 Federal Poverty Income Guidelines 67 .

**** Categorized as being a non-smoker at one or both baseline and wave 3 (first followup examination).

Chapter 5

DISCUSSION

To our knowledge this study is the longest prospective cohort study on dietary sodium intake and BMD that uses modern DXA technology for bone density estimation. A novelty of this sample population is that it covers both a young and older adult age bracket (age 30-64 years). Decreased peak bone mass as a young adult may increase the likelihood of low bone mass in adulthood and old age, thus the inclusion of younger age groups is critical in studying prevention of osteoporosis relative to dietary sodium intake ⁶⁸. Finally, the results of this thesis provide DXA and bone-related dietary nutrient data for an urban minority population of varying education and income, which is an underserved and understudied sub-group for osteoporosis screening and risk assessments ^{22, 69, 70}

The general lack of significant effects for BMD as a function of mean sodium and calcium dietary intake in the mixed models (Table 6) may stem from insufficient data collection time points. Though the time span covered in the analysis is substantial, only two data collection time points is not ideal for a strong statistical growth model. Mean dietary sodium had a significant inverse effect on BMD only at the hip site of AAW, consistent with most of the literature ^{33, 35, 35}. Mean dietary calcium did not have consistent directional effects with BMD across bone sites. The low calcium dietary intake in this sample (AAW 688 \pm 49.4 and AAM 944 \pm 60.2 mg/day) did not appear to

strengthen dietary sodium's effect on BMD as predicted and contradicts previous research that found stronger associations between dietary sodium intake and bone loss when dietary calcium was <506 mg/1000 kcal ³⁶. However, one study in healthy elderly men and women did find that urinary sodium and calcium's parallel excretion and subsequent effects on BMD may only occur at high and moderate dietary calcium intakes, but not at low calcium intakes ³⁹. This could possibly be attributed to varying magnitudes of PTH's action on the renal tubules to increase urinary calcium reabsorption in times of low serum calcium.

Furthermore, it has been shown that African Americans have a higher relative resistance to the bone resorptive action of parathyroid hormone, resulting in higher levels of circulating PTH in response to low serum calcium ^{71, 72}. Thus, despite low dietary calcium intakes, a relatively high level of circulating PTH may allow African Americans to conserve urinary calcium more efficiently than whites. This phenomenon most likely contributes to the larger African American skeleton and possibly to the lack of significant effects seen among dietary sodium and calcium intake and BMD in this sample.

The main effects of dietary sodium and calcium were not statistically significant in the BMD model, but age, smoking and percent body fat yielded significant results. As previously reported, age was a significant predictor for BMD except for the hip site among AAW, which may have been due to small sample size or confounding menopausal status ⁸. Women's fluctuating rates of bone loss may vary up to 2% per year for the 6 to 10 years after menopause, which then taper back to normal rates ⁷³.

Smoking was a significant predictor for AAW with an inverse relationship with BMD at the hip and the spine sites, which is consistent with previous findings ^{74, 75}. Interestingly, body fat percentage was also a direct, significant predictor for lumbar spine BMD in both sexes. It may be that the distribution of body fat is associated with changes in BMD at different bone sites. A study in Japanese women found a similar correlation with lumbar spine BMD and body fat percentage and went on to verify fat distribution's effect by using trunk fat mass to leg fat mass ratios ⁷⁶. Shelton et al. found that self-reported android obesity was associated with hip neck BMD in a group of African American women ⁷⁷. Weight itself has also been previously found to have a significant effect on lumbar spine bone density, but not at more distal bone sites ³³.

Overall, men and women saw a decrease in fat mass between baseline and wave 3 (first follow-up examination). In addition, AAW saw a significant decrease in the percent obese. This decrease may be due to bias caused by the impact of medical test results shared with the HANDLS participants that lead to lifestyle changes after baseline data collection. However, the percent of AAW who are obese in this sample still exceeds the current national average for women according to the CDC (35.8 %) at both time points ⁷⁸. Surprisingly, none of the male participants were classified as obese in this sample. A high percentage of smoking and drug use has been documented in male Baltimore City, Maryland sample population, which may account for the low percentage of obese individuals and may also have implications on bone loss ⁷⁹⁻⁸¹.

The dietary intake of bone-related nutrients in this sample was inadequate compared to the appropriate EAR or AI for each nutrient. Dietary magnesium and

calcium have been found to be inadequate in previous research in this population through the use of mean Nutrient Adequacy Ratios ⁸². Bone-related nutrients tend to be found in higher amounts in fruits, vegetables, nuts and seeds and dairy products, which are not prevalent in the HANDLS population's diet patterns ⁸³. About 53% of HANDLS participants live in low "healthy food availability" areas according to a food availability analysis of surrounding neighborhood stores using NEMS-S (Nutrition Environment Measures Survey–Stores instrument) ⁸⁴. Nutritional inadequacies in the diet increase the risk for osteoporosis and may possibly contribute to the high prevalence of osteoporosis and low bone mass seen in this sample ⁸⁵⁻⁸⁹.

Mean dietary calcium intakes for both men and women (944 \pm 60.2 and 688 \pm 49.4 mg/day, respectively) are below National Health and Nutrition Examination Survey (NHANES) 2009-2010 mean intakes for men and women aged 20 and older (1146 \pm 14.5 and 895 \pm 11.3 mg/day, respectively). However, the mean dietary intake of sodium at wave 3 (first follow-up examination) for AAW (2875 \pm 128.0 mg/day) and AAM (4144 \pm 232.2 mg/day) is comparable to the NHANES 2009-2010 data for men and women aged 20 and older ⁹⁰.

The mean dietary calcium intakes in the HANDLS sample are below the recommended dietary allowance for calcium (1000 mg/day for men over age 19 and women aged 19 to 50 and 1200 mg/day for women over age 50). The mean dietary sodium intakes in the sample exceed recommendations for African Americans set by the 2010 Dietary Guidelines for Americans (<1500 mg/day). However, both the mean

dietary sodium and calcium intakes in this sample are similar to dietary intakes found in the literature that examine association with BMD $^{91, 33, 46, 60}$.

The mean levels of dietary sodium and calcium intake among this HANDLS sample are analogous to other reports that have found strengthened associations between dietary sodium intake and bone mineral density ³⁶. However, despite this inadequate dietary intake of bone-related nutrients, only AAM saw a significant decrease in bone density at the hip and lumbar spine with age. A study examining African American bone density by Sheu Y. et al. estimated an annual 0.42% bone loss at the femoral neck, which is similar to the bone loss rate seen at the total hip in the HANDLS AAM ⁹². However, in the HANDLS sample the mixed models do not suggest that the significant change in BMD was due to sodium's effects, but might be more dependent on age alone.

The lumbar spine BMDs for the HANDLS sample were 0.8 % higher for men and 4.6% higher for women (1.13 (\pm 0.02) g/cm² for both men and women) than the mean African American lumbar spine BMD estimates from a recent CDC report using NHANES 2005-2008 data (men and women BMDs aged 20 and older were 1.121 g/cm² and 1.079 g/cm², respectively; Hologic Discovery, Bedford MA) ⁹³. The total hip BMD for the HANDLS sample was 1.0% lower for men (1.09 \pm 0.01 g/cm²) and 11% higher for women (1.09 \pm 0.02 g/cm²) than the same corresponding African American NHANES 2005-2008 samples' hip BMD (1.101 g/cm² and 0.970 g/cm²). Even though most of the HANDLS sample's mean BMDs exceeded the national average for African Americans (NHANES 2005-2008) as well as whites, the high prevalence of low bone mass and osteoporosis is still a cause for concern. Roughly 21% of this HANDLS sample was

diagnosed with osteoporosis. This percentage is similar to others found in African American sample populations ranging from 4.2% to 44% ^{22, 80, 94, 95}.

African Americans typically have higher BMDs and lower fracture rates than whites, though African Americans may have similar bone loss rates ⁹². Travision et al. found that most of the racial/ethnic differences in BMD could be attributed to patterns in body composition, diet and socio-demographic factors ⁸⁸. Studies have shown that health disparities do exist among minority, lower socioeconomic, urban populations, which may make them more susceptible to common chronic diseases such as osteoporosis and subsequent high fracture mortality rates. These disparities may arise from lack of access to healthcare, lack of trust in healthcare systems, food insecurity, knowledge deficits, or cultural influences ^{20, 70, 96-99}.

Particularly, minority males have been highlighted as an overlooked sub population for osteoporosis risk and screening. The amount of men (18.8%) with osteoporosis in this sample was lower than recent research also conducted in a Baltimore minority urban neighborhood (28.9%)⁷. The young (age 30-50 years) African American men in this HANDLS sample exhibited lower than expected bone density and was a relatively high percentage compared to the women (22% versus 3%). This agrees with a previously found lower ratios of female to male fracture incidence among African Americans compared to whites (1.5 versus 2.9), and an overall higher incidence of male hip fracture in African American men (27.6%) compared to white men (23.9%)^{100 101}.

In addition to diet, racial differences in diabetes prevalence and smoking have been cited as having a powerful effect on African American male BMD ⁹². These health

disparities and co morbidities in minority male populations may not only increase otherwise preventable incidence of bone fracture, but may also impede recovery and increase overall mortality. African American men who sustain a fracture have on average three or more co morbidities while whites typically have one or none ¹⁰⁰. These co morbidities, such as diabetes, hypertension, abnormal gait, or neuromuscular diseases, have been found to be significantly higher in African Americans with osteoporotic fractures, which may also influence recovery¹⁰². A post hip fracture rehabilitation study found that African American men had lower discharge Functional Independence Measure (FIM) ratings when compared to white counterparts ¹⁰³.

While women still sustain more fractures, men have a higher co morbidity burden, especially men of a minority race or ethnicity ¹⁰⁴. In addition, when men do sustain a fracture they are generally less healthy, have high postoperative mortality and are on average, 3-6 years younger than females at time of fracture ¹⁰⁵. This earlier occurrence of bone deficits has implications for AAM BMD as they age, as absolute bone loss and rate of loss is a result of peak bone mass attainment in early adulthood in addition to associated risk factors such as health disparities and co morbidities. In light of this study's results, it may be prudent to study factors that lead to the swift and early decline in bone mass seen among African American men as compared to African American women and whites, especially if these factors also relate to the poor functional outcomes after fracture. Diet was inadequate in this sample and may be a leading contributor to a general lack of health or co morbidity burden associated with the bone loss and prevalence of osteoporosis seen in this male population.

5.1 Strengths & Limitations

A major strength of this study was the use of DXA, a gold standard technique for measuring body composition and BMD. The use of two 24-hour dietary recalls obtained using the validated AMPM provided good representation of usual diet for this sample. This prospective study spans an average of 4.8 years between individual participant's baseline and wave 3 (first examination follow-up), providing a sufficient time lapse for assessment of bone density changes across a young to older adult age range. The extremely thorough HANDLS study methodology included many potential confounders for bone mineral density that were able to be included in analyses.

There are a few limitations to note as well. The sample size was smaller than anticipated due to exclusions and incompletion of wave 3 (first follow-up examination). The current sample may also be a biased subset of the larger HANDLS cohort. Due to the MRV neighborhood schedule, the participants selected for this smaller sample are most likely from the same few neighborhoods visited in the beginning of wave 3 (first follow-up examination). Due to the already small participant sample, individuals with chronic diseases such as diabetes, chronic kidney disease and hyperparathyroidism, were not excluded from the analyses. These chronic diseases, particularly diabetes and end stage renal disease, which are highly prevalent among African American populations, have strong influences on bone mass and fracture risk through natural disease progression 106, 107, 108

Although AMPM is a validated method to measure nutrient intake, it has been reported that obese individuals underestimate dietary intake ¹⁰⁹. Sodium consumed from

salt added at the table is about 5-6% of total consumption and from supplements and medications is less than 1% of total consumption ¹¹⁰. Since approximately 40% of the HANDLS study population use supplements, the lack of supplement data most likely underreported the mean intakes of the selected bone-related vitamins and minerals.

African American bone geometry is different than other races/ethnicities. African Americans tend to have larger bone sizes, which may be a reason that bone densities are higher than other ethnicities on average ¹¹¹. In light of this, a more accurate measure of BMD and accompanying geometry among African Americans would be a 3-dimensional measure (g/cm^3) using volumetric BMD rather than the 2-dimensional areal BMD (g/cm^2) .

Physical activity measures were not available for analysis from baseline data collection and thus were not included as a confounder in the models. The mixed models did not control for menopause status, which also may have impacted the results.

5.2 Future Research

Future research examining the longitudinal effects between dietary sodium intake and BMD should focus on increasing the number of data collection points, control for the aforementioned potential confounders, include supplements in dietary analyses, use volumetric BMD DXA measures, and increase the sample size. Further work in this subject area should always consider the impact of chronic diseases that affect bone such as diabetes, chronic kidney disease, and hyperparathyroidism. It may also be prudent to include multiple 24-hour urine analyses for a more accurate measure of dietary sodium's

effects. Future work may include the use of the Goldberg method to identify under reporters of energy intake ¹¹².

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APPENDIX A

ESTIMATED AVERAGE REQUIREMENTS AND ADEQUATE INTAKE REFERENCES VALUES

ESTIMATED AVERAGE REQUIREMENTS	Males 31- 50yrs	Females 31- 50yrs	Males 51- 70yrs	Females 51- 70yrs
calcium (mg)	800 mg	800 mg	800 mg	1000 mg
Vitamin D (mcg)	10mcg	10mcg	10mcg	10mcg
Magnesium(mg)	350 mg	265 mg	350 mg	265 mg
Phosphorus (mg)	580 mg	580 mg	580 mg	580 mg
ADEQUATE INTAKES				
Sodium (mg)	1500 mg	1500 mg	1300 mg	1300 mg
Potassium (mg)	4700 mg	4700 mg	4700 mg	4700 mg
vitamin K (mcg)	120 mcg	90 mcg	120 mcg	90 mcg

APPENDIX B

RELEVANT HOUSEHOLD SURVEY QUESTIONS (BASELINE ACASI SCRIPT)

Q31. Including wages, salaries, self-employment, and any other source of income we just mentioned, what was your total combined family income during the past 12 months? (Choose one)

0 \$20,000 or more 1 Less than \$20,000 7 Don't Know

Q32. Of the following income groups, which best represents your total household income in the last 12

months? (Choose one)

00 \$0 02 \$1-\$1,999 03 \$2,000-\$2,999 04 \$3,000-\$3,999 05 \$4,000-\$4,999 06 \$5,000-\$5,999 07 \$6,000-\$6.999 08 \$7,000-\$7,999 09 \$8,000-\$8,999 10 \$9,000-\$9,999 11 \$10,000-\$10,999 12 \$11,000-\$11,999 13 \$12,000-\$12,999 14 \$13,000-\$13,999 15 \$14,000-\$14,999 16 \$15,000-\$17,499 17 \$17,500-\$19,999 18 \$20,000 - \$22,499 19 \$22,500-\$24,999 20 \$25,000-\$29,999 21 \$30,000-\$39,999 22 \$40,000-\$49,999 23 \$50,000-\$74,999 24 \$75,000 or more 97 Don't Know

Education Experience (wave 3 (first follow-up examination)ACASI SCRIPT) EDUCHS: Do you have a high school diploma or did you pass a high school equivalency or GED test? Diploma (1) High school equivalency or GED (2) Neither (3)

If EducHS not equal to Neither then go to EducCollege1 **EDUC8GRADE:** Did you attend school past the 8th grade? Yes (1)

No (0)

GOTO Empsay EDUCCOLLEGE1: Did you attend college? Yes (1) No (0)

If EducCollege1 = No then go to Empsay EDUCCOLLEGE2: Did you get a bachelor`s level college degree? Yes (1) No (0)

APPENDIX C

RELEVANT MEDICAL HISTORY VARIABLES & LIST OF MEDICATIONS THAT IMPACT BONE

Variable name	<u>Data</u> <u>type</u>	<u>Data</u> <u>size</u>	
MedHxOTCNDC	Char	10	MedHxMedsOTC: NDC code for medication
MedHxOTCdrugname	Char	100	MedHxMedsOTC: Drug tradename
MedHxOTCdateStart	Num	8	MedHxMedsOTC: Date medication started
MedHxOTCdiagnosisICD	Char	7	MedHxMedsOTC: Disease (ICD-9 dx code) for which drug is taken
MedHxOTCstrength	Char	10	MedHxMedsOTC: Drug strength
MedHxOTCunit	Char	10	MedHxMedsOTC: Unit for drug strength
MedHxOTCfrequency	Char	10	MedHxMedsOTC: Frequency drug taken (qd, bid, etc)
MedHxOTCdosage	Char	10	MedHxMedsOTC: Dosage
MedHxOTCdosageUnit	Char	10	MedHxMedsOTC: Units for dosage
MedHxOTCprn	Num	4	MedHxMedsOTC: Is taken prn (Y/N)
MedHxOTChascontainer	Num	4	MedHxMedsOTC: Participant brought container to MRV (Y/N)
MedHxOTCmedicationId	Num	8	MedHxMedsOTC: LABEL_SEQ_NO
MedHxRxNDC	Char	10	MedHxMedsRx: NDC code for medication

MedHxRxDrugname	Char	100	MedHxMedsRx: Drug tradename
MedHxRxDateStart	Num	8	MedHxMedsRx: Date medication started
MedHxRxDiagnosisICD	Char	7	MedHxMedsRx: Disease (ICD-9 dx code) for which drug is taken
MedHxRxStrength	Char	10	MedHxMedsRx: Drug strength
MedHxRxUnit	Char	10	MedHxMedsRx: Unit for drug strength
MedHxRxFrequency	Char	10	MedHxMedsRx: Frequency drug taken (qd, bid, etc)
MedHxRxDosage	Char	10	MedHxMedsRx: Dosage
MedHxRxDosageUnit	Char	10	MedHxMedsRx: Units for dosage
MedHxRxPrn	Num	4	MedHxMedsRx: Is taken prn (Y/N)
MedHxRxHascontainer	Num	4	MedHxMedsRx: Participant brought container to MRV (Y/N)
MedHxRxMedicationId	Num	8	MedHxMedsRx: LISTING_SEQ_NO

MEDICATIONS THAT IMPACT BONE ¹¹³

Negatively:

- Aluminum-containing antacids
- Antiseizure medicines (only Dilantin® or Phenobarbital)
- Aromatase inhibitors such as Arimidex®, Aromasin® and Femara®
- Cancer chemotherapeutic drugs such as Cyclosporine A, FK506 (Tacrolimus), Methotrexate
- Gonadotropin releasing hormone (GnRH) such as Lupron® and Zoladex®
- Heparin
- Lithium
- Medroxyprogesterone acetate for contraception (Depo-Provera®)
- Proton pump inhibitors (PPIs) such as Nexium®, Prevacid® and Prilosec®
- Selective serotonin reuptake inhibitors (SSRIs) such as Lexapro®, Prozac® and Zoloft®
- Steroids (glucocorticoids) such as cortisone and prednisone
- Tamoxifen® (premenopausal use)
- Thiazolidinediones such as Actos® and Avandia®
- Thyroid hormones in excess.

Positively:

- Calcitriol
- Calcium-sparing thiazide diuretics
- Hormone replacement therapies
- Actonel, Boniva, Fosamax, Reclast
- Prescription micronutrients (i.e. magnesium, potassium, multivitamins, and phosphorus)

APPENDIX D

BODY COMPOSITION OPERATIONS MANUAL

Background and rationale

DEXA bone densitometry is most often used to diagnose osteoporosis, a condition that often affects women after menopause but may also be found in men. Osteoporosis involves a gradual loss of calcium, causing the bones to become thinner, more fragile and more likely to break. The DEXA test can also assess your risk for developing fractures. If your bone density is found to be low, you and your physician can work together on a treatment plan to help prevent fractures before they occur. DEXA is also effective in tracking the effects of treatment for osteoporosis or for other conditions that cause bone loss. Bone density testing is strongly recommended if you:

- 1. are a post-menopausal woman and not taking estrogen,
- 2. have a personal or maternal history of hip fracture or smoking, and
- 3. are a man with clinical conditions associated with bone loss.

Risks

No complications are expected with DEXA procedure.

Limitations

- 1. People with spinal deformity
- 2. Pregnancy
- 3. Obesity

Objective

- 1. To assess the status of the state of the art imaging; techniques in osteoporosis
- 2. To bridge clinical needs and technical means

3. To spread and increase knowledge about strengths and limitations of specific diagnostic techniques

Instrument(s) or assessment tools

Lunar Densitometry DPX machine (serial # MQB+4785)

Equipment and supplies

- 1. Table paper
- 2. Log book
- 3. Scale
- 4. Height measuring tool
- 5. Gowns
- 6. Booties
- 7. Foot brace
- 8. Rice bags
9. Ceram wrap

10. Velcro straps

Participant and exam room preparation

- Have the participant remove any attenuating material. This includes, but is not limited to, any clothing with metal or plastic, jewelry, shoes, brassieres, belts or glasses. Usually this requires participants to change into hospital gowns.
- Have the participant sit upright on the center of the table so that the center line on the pad runs through the center of the pelvis on the participant. To make sure that the participant is centered, determine if their spine is lined up the center line.
- Have the participant lay on their back. Make sure that the participant is still centered on the table.
- Use the caliper to measure the participant thickness in the stomach area. Then select the appropriate scanning mode for the AP Spine measurement.

Note. If the participant is large in the stomach area, pull the belt that is along the side of the table across the participant to minimize the height of the tissue in that area.

Detailed measurement procedures

The first one arriving in the morning should do the daily Quality Assurance (QA) on the DEXA using the Lunar spine phantoms. This QA must be run before any scans are acquired. Print a report for each QA scan and file it in a locked file cabinet.

In case of any technical problems with the scanner, call Lunar at 800-344-5831 or 608-274-2663 and ask for an application specialist.

Our system number is MQB+4785.

Daily test procedures for the DEXA

A QA test must be run daily before performing any bone scans. The QA test verifies the correct operation of the densitometer. The QA test examines the functionality, as well as the accuracy and precision of the densitometer. The QA takes approximately 15 minutes to complete with less than one minute of operator intervention involved.

Performing the QA test

- Select QA from the main screen {F3}
- Clear all objects of the tabletop. Pull back the pad for the head of the table. Position the standard block so that the brass colored part is upward and away from the center of the table.
- Select {Esc}.
- Select any key to make sure that the shutter lights are one. If the lights are on, select Y to begin QA.

- The remainder of the QA runs automatically. The program will automatically print out the results.
- Print a report for each QA scan and file in a locked file cabinet.
- Review QA scan reports weekly to detect drift.
- Test QA after any change in software, moving the machine, change in room temperature, etc.
- Make sure that all test pass. If the printout shows a failed result, run the QA again. If all tests do not pass the second time, contact Lunar at 800-344-5831or 608-274-2663.

Phantom measurements

A spine phantom measurement must be run daily. The spine phantom mimics the typical size and density range of a normal human spine. The phantom consists of the L1 through L4 vertebrae with $\frac{1}{2}$ of T12 and L5 as landmarks.

Performing the phantom measurements

- Press {F1}, Scan participant on the AP Options screen.
- Select the "Spine Phantom" participant.
- Press {Esc}.
- Press {F1}, Verify Values. The mode should be on medium, 750 current.
- Press {F1}.
- Fill the water bath container with 15cm of room temperature tap water and put the container lid on securely. Transfer the filled container to the scan table. Place it in the center of the table, even with the location of the participant's compressor strap, and remove the lid.
- Place the spine phantom in the center of the bottom of the container. Position the phantom so the T12 is nearest the head end of the table and L5 is nearest the foot end of the table.
- Press {Esc}. The scan arm and detector move to the Home position.
- Press {Esc}. The scan arm and detector move to the approximately starting position.
- Position the localizer light over the middle region of L5. Align the localizer light with center of the spine phantom.
- Press {Esc} to start the scan. The scan should begin in L5 and move up the phantom. The detector must not pass the outer edges of the container and move into air at any time

during the scan. If the detector is not properly positioned, press $\{F1\}$ to abort the scan. Follow the screen prompts to reposition the detector and restart the scan.

- Allow the scan to run until 3 lines of T12 are visible. Press {F1} to end the scan. Follow the screen prompts to save the scan.
- When the scan is finished, place the lid on the container and remove it from the table. Remove the phantom from the container and dry is with a soft cloth. Drain the water from the container.

Analyzing the spine phantom scan

- Press {F2}. Analyze Scan, on the AP Spine Options Screen.
- Select the appropriate "Spine Phantom" to analyze.
- Press {Esc}.
- Press {F2}. Auto Analysis. Determine if there are 88 lines between L2 and L4. To accomplish this, use the up and down arrows to view the line number of each intervertebral space. The space number of L2 should be 95 and the space number of L4 should be 7. If this is not correct, press {F2}, then us the up and down arrow to move the space markers to correct the line number.
- Press {Esc} to save the changes you made to the invertebral spaces.
- Press {Esc}. The Analysis Results screen appears.
- Press {F2} to save changes.
- Print the results.
- To verify that there was correct positioning, the height of L2-L4 on the Ancillary printout should be 10.56.
- Print a report and file it in the Phantom log book kept in the cabinet above scanner.

Performing Total Body Scans

Landmarks

Scanning modes for total body, femur, and spine.

Total body. Use the caliper to measure the participant's thickness in the stomach area.

Spine. Use the caliper to measure the participant's thickness in the stomach area.

Femur. Use the caliper to measure the participant's thickness in the stomach area. Set mode as shown in Table 1.

Weight and height limits for Bone Scan Acquisition

9.8-77 inches (25-196 cm) in height 80-250 lbs (36-113 kg) in weight

*Spine: Width- 180 auto Length- 200 manual

To enter a new participant:

- Main menu {Fl} scan participant.
- Press {F4} on this menu to enter participant name, height, weight, etc.
- Press {Fl} from this menu to go to optional information
- Fill in ID number and your initials.
- Press {Esc} key to take you to the scan to be done.

Settings

Mode and length settings for total body, AP spine, and femur are shown in Table 2. (5-15 lines of iliac crest) (25-40 lines to ischium) To set up computer to a particular scan (e.g., Total Body):

- Main menu F6, then page up to desired scan.
- Press {Esc} key and this returns you to the main menu.
- Press {Fl} scan participant, Fl to search and Fl for optional information.
- Press {F1}, Scan Participant on the Total Body Options Screen.
- Add a new participant to the Participant Directory or select an existing participant. Press {Esc}.
- Enter the mandatory information for a new participant, or verify the mandatory information for an existing participant.
- Press {F1}, Optional information, to enter optional information for a new participant or to verify the optional information for an existing participant.
- Press {Esc}.
- Press {Esc}. The scan arm and detector move to the Home position.
- Have the participant sit upright on the center of the table so that the center line on the pad runs through the center of the pelvis on the participant. To make sure that the participant is centered, determine if their spine is lined up the center line also.
- Have the participant lay on their back. Make sure that the participant is still centered on the table.
- The top of the head should be 1 to 2 cm from the top line on the pad.
- Hands palm down or palms along the side of the leg. Arms tucked against hips and within the outside lines of the pad.

- Strap the participant's feet and knees together with Velcro straps.
- Use the caliper to measure the participant's thickness in the stomach area. Then select the appropriate scanning mode for the Total Body measurement.

Note. If the participant is large in the stomach area, pull the compressor strap that is located along the side of the table across the participant to minimize the height of tissue in that area. Scanning modes for total body by participant's size are shown in Table 3.

- Press {F1}, Verify Values, to check the scan values.
- The mode window appears.
- After checking or changing the mode setting, according to the participant's thickness, press {Esc}.
- Press to return to the Total Body Acquisition screen. The scan begins.

Analyzing total body scans

Analyzing femur scan

- Press {F2}, Analyze Scan, on the Femur Option Screen. Select the participant to be analyzed.
- Press {Esc}. The participant information screen appears.
- Press {Esc}. The scan image appears.
- Verify correct positioning: femur is straight, lesser trochanter is not or minimally visible.
- Press {F2}, Auto Analysis, to examine the Neck ROI position. Refer to the following for correct position of the Neck ROI.
 - 2 Soft tissue should be contained in all four corner of the ROI.
 - The ROI is perpendicular to the femoral neck.
 - ² The ROI, ideally, should not contain part of the ischium.
 - ² The ROI does not include any portion of the trochanter.
- If the position of the Neck ROI is not correctly positioned, follow these instructions.
 - \square Select {F2} from the Bone Results screen.
 - \square Select {F1} to move, {F2} to expand, or {F3} to rotate the ROI to perpendicular to the axis of the femoral neck near the top end of the femoral neck
 - \square Select {F9}, then {Esc}.

• Press {Esc}. Save and print results.

Performing AP spine scans

Scanning modes for AP spine by participant's size are shown in Table 4.

- Press {F6} to access scanning mode for AP spine.
- Press {Esc}. The scan arm and detector move to the approximate starting position.
- Have the participant bend their legs. Lift the participant's legs onto the support block. The support block should be positioned so the participant's thighs are at a 60-90 degree angle for their spine. The edge of the block should be located directly under the bend of the knees.
- Have the participant point to their navel. Position the laser light approximately 2 inches below the navel.
- Press {Esc} to start the scan. Monitor the first few lines to verify that the detector is properly positioned. You should scan approximately 5-15 lines of iliac crest. The top of L5 should appear in the scan. If the detector is not properly positioned, press {F1} to abort the scan. Follow the screen prompts to reposition the detector and restart the scan.
- Allow the scan to run until you see where the ribs of T12 touch on each side of the spine.

Analyzing AP spine scans

- Press {F2}, Analyze Scan, on the Total Body Screen. Select participant to analyze from the appropriate database.
- Press {Esc}. The participant information screen appears.
- Press {Esc}. The scan image appears.
- Press {F1}, Verify Values, adjust the Grey Scale until enough tissue is visible.
- Press {F1}. The scan image appears.
- Press {F2}, Auto Analysis.
- Press {F2}, Extended Research.
- Use arrow keys to move through the list of cuts to modify. Modify the cuts by using the arrow keys. Refer to the following cut positions to correctly modify the scan.
 - I Head: Position immediately below the chin.
 - Left and Right arms: Both arms cut pass through the shoulder sockets and are as close to the body as possible. Ensure the cut separates the hands and arms from the body.

- Left and Right Spine: Both spine cuts are ass close to the spine as possible without including the ribs.
- Left and Right Pelvis: Both pelvis cuts pass through the femoral necks and and do not touch the pelvis.
- 2 Pelvis Top: Position immediately above the top of the pelvis.
- 2 Left and Right Leg: Both leg cuts separate the hands and forearms from the legs.
- Center Leg: Separates the right and left leg.
- 2 Center Cut: This line runs through the center of the entire body.
- Press {Esc} to save changes.
- Press {Esc}, Save and Print.

Performing femur scans

- Press {F2}. Analyze Scan, on AP Scan Option Screen. Select the participant to be analyzed.
- Press {Esc}. The participant information screen appears.
- Press {Esc}. The scan image appears.
- Verify that T12 and L5, the top of both iliac crest, are visible.
- Press {F2}. Auto analysis to check the labels and placement of analysis regions. Make sure Ll through L4 are correctly labeled. (Number from L4 upward.) If not, press {F3}. Use the arrow keys to select the correct labels. If markers are missing, press {F4}, insert markers. Make sure the program has correctly positioned the intervertebral space markers. The space markers are between the vertebral bodies and located at the lowest point of bone density. Use the Up/Down arrow keys to move the markers up or down. Use the Right/Left arrow key to rotate the markers. Examine the edge markers by pressing {F7}. Make sure the edge markers are positioned above the baseline to include only high-density points. Do not include soft tissue points in the analysis region. To accomplish this, press {F3}, recalculate edges. Use the Up/Down arrow keys and the program will reposition the edges.
- Press {Esc}. Save and print the scan.
- Press {F6}.
- Scanning Menu Option Box will appear. Select Femur.
- Press {Esc}. The scan arm and detector move to the Home position.

- Have the participant lay on their back. Make sure that the participant is still centered on the table.
- Use the caliper to measure the participant's thickness in the femur area. Then select the appropriate scanning mode for the Femur measurement.
- Scanning modes for femur by participant's size are shown in Table 5.
- Locate the participant's great trochanter and position the localizer light approximately 2 inches below the greater trochanter. This can also be accomplished by locating the bottom of the pelvis bone, positioning the localizer light approximately 2 inches below it and should be in the middle of the thigh.
- Position the foot brace in the center of the scan table. Use the centerline on the pad as a reference. Strap the participant feet to the foot brace. Make sure that the entire leg is rotated to the angle of the brace. To accomplish this, turn the participant's knee inward until properly rotated. The strap must be fastened tightly to maintain this position.
- Place one rice bag flat on the table, tight to the participant's leg. Place the other rice bag tight against the leg to prevent air gaps.
- Select {Esc} to start the scan. Monitor the first few lines to make sure that the detector is properly positioned. You should scan approximately 25-40 lines before seeing the ischium. There should be little to no lesser trochanter showing. If too much of the lesser trochanter is showing, the participant's leg must be rotated more. If the detector or the participant is not properly positioned, press {F1} to abort the scan. Follow the screen prompts to reposition the participant and detector. Restart the scan.

Maintenance of equipment

Table pads must be laundered bi-annually by the Logistics staff. Table pad paper and Saran wrap must cover head --> mid-chest of participant.

Personnel qualifications

Training Requirements Certification Requirements Certification Checklist

APPENDIX E

INFORMED CONSENT FOR BASELINE HANDLS

IRB number: 2009-149

Clinical Site Version: 08/01/2011

Project Title: Healthy Aging in Neighborhoods of Diversity Across the Life Span – Wave 3

Principal Investigator: Michele K. Evans, MD Institution: National Institute on Aging, NIH

Informed Consent for Clinical Research HANDLS Wave – 3

SPONSOR:	NATIONAL INSTITUTE ON AGING, NIH
SPONSOR:	NATIONAL INSTITUTE ON AGING, NI

Mobile Medical Research Vehicles (MRVs) Neighborhoods in Baltimore City

INTRODUCTION

SITE:

We invite you to take part in the next phase of a National Institute on Aging (NIA) research study called Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS). You were selected as a participant in this study because when we were looking for residents from 30 and 64 years old in your neighborhood you decided you wanted to take part in the study. It is time for us to return to your neighborhood for the first follow-up examination. You now have an opportunity to decide whether you would like to participate in the next phase of HANDLS. You will notice that some of the tests are the same as the last time we saw you. We have added some different tests and questionnaires that you might not be familiar with. Please take your time to read this form. Be sure to ask any questions you may have before making your decision. We encourage you to discuss your decision with your family, friends and your doctor(s).

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to learn about changes in health over time in an urban group of African-American and white men and women residing in Baltimore city. Our goal is to study health change, as people grow older. We plan to do this by studying many people in different neighborhoods and the same people over many years. This gives us the information we want about how peoples' bodies change over time.

We also want to study why some people are healthier than others as they get older. We want to discover if we can predict the causes of good health with aging and if we can find better ways to prevent and treat disease. If we can find the causes of good health, then we might find cures for some of the diseases related to aging. This is a research study where we will follow you over the next twenty years to see how you age. This will help us learn about diseases like heart disease, Alzheimer's disease, high blood pressure, diabetes and stroke. We are trying to understand why some Americans have higher rates of certain diseases and more severe diseases than other Americans.

MedStar Health Research Institute	Consent To Participate In A Medstar Health Research Institute Clinical Research Study Page 1 of 15	IRB Approval Stamp (ORAUSE ONLY - DO NOT CHANGE ANY INFORMATION THIS SECTION) Med Star Health Research Information this section, APPROVAL DATE SEP 272012 SEP 262013 APPROVAL EXPIRES
	Participant Initial	IRB APPROVED Form Revision Date: 05/10/04

 IRB number:
 2009-149
 Clinical Site Version: 08/01/2011

Project Title: Healthy Aging in Neighborhoods of Diversity Across the Life Span – Wave 3

Principal Investigator: Michele K. Evans, MD Institution: National Institute on Aging, NIH

WHAT ELSE SHOULD I KNOW ABOUT THIS RESEARCH STUDY?

It is important that you read and understand several points that apply to all who take part in our studies:

- Taking part in the study is entirely voluntary and refusal to participate will not affect any rights or benefits you normally have;
- You may or may not benefit from taking part in the study, but knowledge may be gained from your participation that may help others; and
- You may stop being in the study at any time without any penalty or losing any of the benefits you would have normally received.

The nature of the study, the benefits, risks, discomforts and other information about the study are discussed further below. The information is also explained in the informed consent booklet that goes with this consent form. If any new information is learned, at any time during the research, which might affect your participation in the study, we will tell you. We urge you to ask any questions you have about this study with the staff members who explain it to you and with your own advisors before agreeing to participate.

WHO IS IN CHARGE OF THIS STUDY?

The research is being conducted and sponsored by the National Institute on Aging with Michele K. Evans, M.D. and Alan B. Zonderman, Ph.D. as the primary investigators. All clinical research involving human subjects is required under regulatory guidelines to be reviewed by an Institutional Review Board (IRB). An IRB performs critical oversight functions for research conducted on human subjects that are scientific, ethical, and regulatory. The NIA has hired the MedStar Health IRB to perform this service.

WHO CANNOT PARTICIPATE IN THIS STUDY?

You cannot be in this study if any of the following apply to you:

If you:

- Did not give your consent to be in the HANDLS Wave 1study during the recruitment phase
- Do not have a valid picture ID
- Are unable to give informed consent
- Are pregnant
- Are currently undergoing cancer treatment (chemotherapy or radiation)
- Have undergone cancer treatment (chemotherapy or radiation) within the last 6 months

MedStar Health		
Kestartii institute	Consent To Participate In A Medstar Health Research Institute Clinical Research Study	IRB Approval Stamp Medicial Freak Research Institute APPROVAL DATE
	Page 2 of 15	APPROVAL EXPIRES IRB APPROVED Form Revision Date: 05/10/04

IRB number:	<u>2009-149</u>	Clinical	Site Version: 08	8/01/2011		
Project Title:	Healthy Aging in Neighborhoods of Diversity Across the Life Span – Wave 3					
Principal Inves	stigator:	Nichele K. Evans, MD	Institution:	National	Institute on Aging	g, NIH
WHAT IF I AM	PRESENTL	Y PARTICIPATING IN ANO	THER RESEARC	H STUDY?	2	
Are you presen	tly particip	ating in any other research s	tudies? Y	es 🗌	No 🗌	
If yes, p	lease state w	hich study (ies)				

While participating in this study, you should not take part in any other research project that in the judgment of the principal investigator is incompatible with this research study. This is to protect you from possible injury arising from such things as extra blood drawing, extra x-rays, interaction of research drugs, or similar hazards.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 3721 people will take part in this study, around 300 from your neighborhood.

WHAT HAPPENS IF I AGREE TO BE IN THE STUDY?

The HANDLS Wave 3 study data will be collected in two parts. You are required to give your consent to be able to participate in the study. The first part of the study is the examination visit to the mobile Medical Research Vehicles. The second part of the study is a telephone interview that will happen 7-10 days after your examination visit. You may also be invited to participate in a third part of HANDLS Wave 3. The third part of HANDLS Wave 3 consists of two additional studies to be conducted at Harbor Hospital and the University of Maryland. You will learn more about those studies during this examination visit, if you are eligible to participate. You will be asked to sign a separate consent form at Harbor Hospital and/or at the University of Maryland, if you decide to join either of those studies.

This is the consent form for HANDLS Wave 3. You will be asked to give your consent for all of the procedures and interviews that make up Wave 3 of HANDLS. Specifically, we want to be sure you understand the nature of research we are doing and what is being requested of you. It is also important that you understand any potential risks to you. You may participate in any of the tests, but you do not have to participate in all of the tests. Choosing not to participate in a test will not affect your right to participate in the rest of this study. You may stop any test after it starts. If you are unable to complete all of the tests in one visit you may be invited to return to the MRVs to complete your testing.

For the first part you will be required to spend a day at our Mobile Medical Research Vehicles (MRVs) to have testing. You will be asked provide an update about your medical history since your last examination and you will receive a physical examination. We will ask you to remember all of the food you ate the day before your visit. We will assess your muscle strength and bone density. You will have a test to check the blood flow in your heart and to see if your heart valves are leaking. We will also ask you to complete a questionnaire and to participate in memory

MedStar Health Research Institute	Consent To Participate In A Medstar Health Research Institute Clinical Research Study	IRB Approval Stamp (ORA USE ONLY - DO NOT CHANGE ANY INFORMATION IN THIS SECTION) MedStar Health Research Institute APPROVAL DATE SEP 2 7 2012 SEP 2 6 2013
	Page 3 of 15	
	Participant Initial	Form Revision Date: 05/10/04

IRB number:	2009-14	<u>2</u> Clinical Si	Clinical Site Version: 08/01/2011		
Project Title:	:t Title: Healthy Aging in Neighborhoods of Diversity Across the Life Span – Wave 3				
Principal Inves	tigator:	Michele K. Evans, MD	Institution:	National Institute on Aging, NIH	

testing. You will be asked about activities of daily living, use of health care services, and any income and/or employment changes since your last visit to the MRVs. We will also take blood, tissue and urine samples.

The blood draw will be performed right before you are served breakfast. We will use these samples to measure your health and so that we can measure changes in your health if we test you again. We will measure your white and red blood cells, your cholesterol, salt, and sugar, and how well your blood carries oxygen through your body and how fast you heal from minor cuts. We will also measure blood chemistry that may tell us how well your body organs work, such as the heart, liver, and kidneys. Women between the ages of 30 and 55 years will get a pregnancy test. We will be testing for communicable diseases including Hepatitis B, Hepatitis C, and Syphilis.

As part of this study, you will be offered a test for the human immunodeficiency virus (HIV). This is the virus that causes AIDS. If you are infected with HIV you will still be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report newly diagnosed HIV infection, and the importance of informing your partners of the possible risk because of your HIV infection. If you decide to have the test, you will be asked to sign a separate consent form. It will explain the HIV testing procedures for the HANDLS study.

You will also be asked to give a DNA sample by using a method that collects cells from a saliva (spit) sample you provide. Before you agree to give the DNA sample you will be required to review the information below that explains the procedures and risks of providing DNA samples. More details about the specific testing for this part of the study are described below.

The tests involved in this study are described in the attached **Consent Booklet**. All of the tests are performed for the purpose of research and are not designed to improve your health at this time. There are no experimental medications, tests or procedures in this study. We perform these tests free of charge. If, after reading the **Consent Booklet**, there are tests in which you do not wish to participate, please list them on the back of this form.

Below is a table that shows the tests you will be expected to complete. This chart also tells you how long we think it will take each test to be done and in which vehicle it will be given.

Phase 1 – Medical Research Vehicle Examination

Measure or Procedure	Estimated Timing	Location
Consent Specimen Collection (Urine, Blood, DNA) Anthropometrics (height & weight)	20 minutes 20 minutes 5 minutes	MRV2/3 MRV 3 MRV 1

MedStar Health Research Institute

Consent To Participate In A Medstar Health Research Institute Clinical Research Study

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Participant Initial



IRB number: 2009	-149 Clinica	nl Site Version: 08/01	1/2011
Project Title: Healt	thy Aging in Neighborhoods of D	iversity Across the Lif	ife Span – Wave 3
Principal Investigato	or: Michele K. Evans, MD	Institution: N	lational Institute on Aging, NIH
Interim Medical Histo Interim Physical Exar Dietary Recall I Cognition Physical Performance Echocardiogram Questionnaires Sectio Test of Financial & He Body Composition/B	ory m e on A ealth Literacy one Densitometry	20 minutes 20 minutes 30 minutes 40 minutes 15 minutes 20 minutes 30 minutes 30 minutes	S MRV 1 S MRV 1 S MRV 2 S MRV 2 S MRV 1 S MRV 1

Phase 2 - Telephone Interview

The HANDLS wave 3-telephone interview is designed to take place after your visit to our Mobile Medical Research Vehicles (MRVs). We will ask you to complete an interview over the phone. We are contacting everyone from the study to see if they would like to take part in this telephone interview. It should take about 40 minutes to complete.

The telephone interview is a dietary recall questionnaire that asks you to remember what you had to eat and drink in the last 24 hours. We will use pictures to help you give us information about how much food and drink you had in the last 24 hours. You may remember the dietary recall interview from your visit to the MRVs. The difference for this interview is that we will conduct the interview over the phone. All materials (pictures, etc.) for the phone interview will be delivered to you by US mail or given to you at the end of your MRV visit.

The telephone survey is used to collect information for our research. It is not designed to improve your health at this time. We perform the telephone survey free of charge. You may participate in telephone survey, but you do not have to. You may stop the survey after it starts. This will not affect your right to participate in the other parts of the HANDLS study. If you stop the questionnaire we will still invite you for your next MRV examination.

HOW LONG WILL I BE IN THE STUDY?

We think you will be in the study for the next 15 years because this is a longitudinal study that follows your health over time as you age. This is a study that provides long-term follow up. The study doctor or the National Institute on Aging may stop your participation in this study at any time without your consent. You can stop participating at any time. However, if you decide to stop participating in the study, we ask you to talk to the researchers first.

MedStar Health		
Research Institute	Consent To Participate In A Medstar Health Research Institute Clinical Research Study	IRB Approval Stamp NedStar Health Research Institute APPROVAL DATE SEP 272012
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IRB number:	2009-14	Clinical Site Version: 08/01/2011		
Project Title:	Healthy Aging in Neighborhoods of Diversity Across the Life Span – Wave 3			e Life Span – Wave 3
Principal Inves	tigator:	Michele K. Evans, MD	Institution:	National Institute on Aging, NIH

WHAT ARE THE RISKS AND SIDE EFFECTS OF THIS STUDY?

If you decide to participate in this study, you should know there may be risks. The risks for this study are minimal. The descriptions of the tests given on the Mobile Medical Research Vehicles include any risks and other possible side effects. They are also explained in the **Consent Booklet** under the Assessment of Risks section. Potential risks and side effects related to this study include:

We want you to know that there are some risks in donating a blood sample. The trained HANDLS staff member will insert a needle in a vein in your arm. There is a risk of an infection from the needle puncture. There is also a risk of a black and blue mark, and you may feel faint. These risks are very small. Our staff is well trained and has drawn blood many times. It is common to have a small black and blue mark, but it disappears after a day or so. Some people have begun perspiring, or they felt nauseated and their pulse slowed. None of them had any after effects.

This research study requires a small amount of radiation from the DEXA Scan. It must be noted that this radiation exposure is not needed for your medical care. It is for research purposes only. The total amount of radiation you will receive from this study is from one DEXA scan. The NIH Radiation Safety Committee has reviewed the use of radiation in this research study. It has approved this use as involving minimal risk and needed to obtain the research information desired.

Using the standard way of describing radiation exposure, from one DEXA Scan you will receive an effective dose of less than one thousandth of one rem. By comparison the average person in the United States receives this much radiation every day from natural sources, such as the sun. In this scan the only part of the body exposed is the skin, which is less sensitive to radiation than other parts of the body. There is a very small risk of cancer from the x-rays in DEXA scan, but is too small to measure.

If you are pregnant you may not participate in this study. Unborn babies are more sensitive to radiation than children or adults.

The risks for the dietary recall interview, the questionnaires and memory testing are very minimal. The only risk of this part of the study is that you may become tired and sometimes, people feel nervous when they do these tests. All examiners who are involved in giving these tests are experienced in using these procedures and they will minimize any discomfort that you might feel. If the tests are disturbing you, then you may stop testing any time you want.

For more information about risks and side effects, you should call the Principal Investigator, Michele K. Evans, M.D. at 410-558-8573.

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Kocarch Holitak	Consent To Participate In A Medstar Health Research Institute Clinical Research Study	IRB Approval Stamp (ORA USE ONLY - DO NOT CHANGE ANY INFORMATION IN THIS SECTION) MedStar Health Research Institute APPROVAL DATE <u>SEP 272012</u>
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IRB number:	<u>2009-14</u>	<u>9</u> Clinical	Clinical Site Version: 08/01/2011		
Project Title:	Healthy	Aging in Neighborhoods of Diversity Across the Life Span – Wave 3			
Principal Inves	stigator:	Michele K. Evans, MD	Institution:	National Institute on Aging, NIH	

GENETICS AND DNA TESTING

INFORMATION - WHAT HAPPENS IF I AGREE TO PARTICIPATE IN GENETICS TESTING

The purpose of this section of the consent form is to give you information regarding a blood and saliva sample requested as part of your participation in the HANDLS research study. The blood and saliva sample will be used in the genetic research described below. Genes are pieces of information that you get from each parent and are found in every cell in your body. For example, different genes are responsible for hair or eye color.

More and more, we are discovering that our genes are important for understanding our health. We will study genes and parts of genes that may cause age related diseases or make these diseases more severe. By finding out the genes that cause specific conditions associated with aging, we may be able to find ways to prevent certain diseases, find them at an earlier and milder stage, or at least be able to treat these conditions better. This study is particularly interested in genes that may be involved with loss of memory, high blood pressure, heart disease, stroke, cancer, diabetes, and arthritis.

PROCEDURES FOR GENETICS/DNA TESTING

You will be asked to give a DNA sample by using a method that collects cells from a saliva (spit) sample you provide. We also want to use some of your donated blood to freeze your DNA. We are not sure what studies will use your DNA. New studies may look at how your genes affect age-related diseases. If you decide not to participate in genetic testing, you will still be considered for the clinical research study.

WHAT ARE THE RISKS OF PROVIDING DNA SAMPLE

As part of the HANDLS study you are being asked to be in the part of the study involving genetic testing. Discomfort and inconvenience associated with participation in this part of the study come from the methods used for obtaining the blood needed to obtain the genetic sample. We expect that any discomfort you experience will be minimal. To obtain a blood sample, the needle stick may cause bruising at the site the needle goes into the skin. Fainting and, in rare cases, infection may occur. These events are easily treatable and reversible.

There are no known risks associated with the procedures used to collect the DNA (saliva) sample.

The more serious risk of genetic testing includes the possible misuse of personal, genetic information. Although rare, misuse of such information has caused problems for persons related to employment, life, or health insurance benefits and right. There is a risk that being in a genetics study can cause psychological distress or tension with other family members. Although there can be no absolute guarantees, every reasonable effort will be made to keep your personally identifiable information secret so that there will be no misuse. Even when the information is kept

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IRB number:	2009-14	009-149 Clinical Site Version: 08/01/2011		
Project Title:	Healthy Aging in Neighborhoods of Diversity Across the Life Span – Wave 3			e Life Span – Wave 3
Principal Inves	tigator:	Michele K. Evans, MD	Institution:	National Institute on Aging, NIH

secret, if you are asked if you have ever been tested for a genetic disorder, answering "yes" could cause benefits to be denied or could cause other problems including discrimination.

For more information about risks and side effects, you should call the Principal Investigator, Michele K. Evans, M.D. at 410-558-8573.

Please initial by the line indicating your wishes about participating in genetics/DNA testing:

I consent to the DNA collection

I do NOT consent to the DNA collection

WHAT WILL HAPPEN TO MY SAMPLES WHEN THE STUDY IS OVER?

The NIA will retain custody of your samples for studies as outlined above. You will retain the right to have the sample material made unavailable for future genetic testing and other specific testing by completing the section below by initiating on the line next to your choice. The NIA will be the exclusive owner of any data, discoveries or derivative materials from the sample materials and is responsible for the restriction of sample use at your request. If a potential commercial product is developed from this research project, the NIA will develop patents and promote commercialization of the product as required by law. You will not profit financially from such a product.

Doctors often make new discoveries by testing blood and urine. We would like to freeze a portion of your blood and urine samples to save them in our frozen tissue bank. We are not sure what new discoveries will appear in the future. We want to set aside your samples until there are new tests that will help us understand health and aging.

The samples saved in our bank will be stored at very low temperatures. Unlike household freezers, these freezers can preserve samples for many years, perhaps many decades. We will label your samples with code numbers. Only the principal investigators in this study will know your code number. Only researchers in this study will know the results of tests using your genes. We will not reveal your results to anyone who is not part of this research.

We will ask you if you want the results of the tests that we perform on your blood and urine. We will also ask you if you want us to send your results to your personal physician. We do not plan to report the results of the studies we do on your genes because at this time, these tests do not diagnose or predict the development of specific diseases. In the future, we may offer you some of the results if the Food and Drug Administration approve some of the tests.

Your samples will be stored in secured freezers at an NIA facility. Your name and identifying information will be removed and we will give the samples a code. The key to the code will be kept in a separate, secure area.

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	Participant Initial	Form Revision Date: 05/10/04

Project Title: Healthy Aging in Neighborhoo	Healthy Aging in Neighborhoods of Diversity Across the Life Span – Wave 3		
Principal Investigator: Michele K. Evans, N	Institution:	National Institute on Aging, NIH	

Your samples will be used only for the study described in this consent form unless you give us permission to use them for other studies.

If a future research project arises where your samples could be useful, we ask you to designate as to whether or not your sample can be used. Any future research use will require approval by the Institutional Review Board (IRB).

Please initial by the line indicating your wishes:

____YES, I give permission to use my (blood or other fluids, tissues) samples in future research studies under the following conditions:

_____These samples may be used for other research projects without contacting me only if the identification code is removed so that the sample can no longer be identified as mine

These samples may be used for other research projects without contacting me even if the code is left on the samples. I understand that if the samples are coded, they may be able to be traced back to my personally identifiable information and my medical records.

____MAYBE, I wish to be re-contacted if further studies with my samples are considered. After the study has been explained, I will then decide if I want my samples to be included.

_____NO under no circumstances shall my samples be used for any future studies. My samples should be discarded once the present study is complete.

If you allow future research on your sample and the research provides information important for your health, we will try to contact you. If you wish to be contacted please keep the principal investigator for this study or the NIA updated about changes in your address or phone number.

HOW WILL I FIND OUT ABOUT THE GENETICS/DNA RESULTS OF THE STUDY?

The Genetics studies we do are to add to our knowledge of how genes and other factors affect the long-term health of minority and medically underserved populations. We are gathering this knowledge by studying groups of people, and the study is not meant to test your personal medical status. For these reasons, we will not give you the results of our research on your sample. If you have questions about whether any genetic tests would be useful to you, you should ask your doctor.

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Project Title:Healthy Aging in Neighborhoods of Diversity Across the Life Span – Wave 3Principal Investigator:Michele K. Evans, MDInstitution:National Institute on Aging, NIH	IRB number:	2009-149	2 Clinical Si	te Version: 08	3/01/2011
Principal Investigator: Michele K. Evans, MD Institution: National Institute on Aging, NIH	Project Title:	Healthy /	Aging in Neighborhoods of Diver	sity Across the	Life Span – Wave 3
	Principal Inves	stigator:	Michele K. Evans, MD	Institution:	National Institute on Aging, NIH

ARE THERE ANY BENEFITS TO TAKING PART IN THE STUDY?

This study is not designed to give direct benefits to any participants. If you agree to take part in this study, there may or may not be direct medical benefits to you. We hope the information learned from this study will benefit others in the future. There is no charge for any of the testing described. You may benefit by learning more about your health, or possibly from learning that you have a condition or problem. You will receive a Participant Report Package in the mail, with results of your visit to the MRVs. If the study doctor discovers any condition or problem, the information will be provided to you and your doctor, if you authorize it. To authorize the reporting of results to your physician you will need to sign a form called "Release of Medical Information". You will be asked to sign this form only if you want us to communicate with your physician. The study doctors do not provide medical treatment.

WHAT OTHER OPTIONS ARE THERE?

There are no other options associated with your participation in this study. You may choose either to participate or not to participate in this research. Taking part in this study is entirely voluntary. You may choose to withdraw from the study at any time.

WHAT ABOUT CONFIDENTIALITY?

When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example for an insurance company, the NIH will give the insurance company information from your medical records. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Privacy Act protects the confidentiality of your NIH medical record. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

You will be asked to sign a separate consent form, Health Insurance Portability and Accountability Act (HIPAA), that will give permission to the investigator and sponsor (which is NIA/NIH), and certain other people, agencies or entities to look at and review the records related to this study including your personal health information (PHI) and the information discovered during this study. If you do not wish to sign this permission form you will not be allowed to participate in this study.

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Project Title:	Healthy Aging in Neighborhoods of Diversity Across the Life Span – Wave 3			e Life Span – Wave 3	
Principal Inves	tigator:	Michele K. Evans, MD	Institution:	National Institute on Aging, NIH	

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this certificate the researchers cannot be forced to disclose information that may identify you, even by court subpoena, in any federal, state, or local civil, criminal, administrative, legislative or other proceedings. The researchers will use the certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the U.S. Department of Health and Human Services that is used for auditing or program evaluation or for information that must be disclosed in order to meet federal regulations.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researcher may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following conditions: It does not apply to state requirements to report certain communicable diseases. In addition, the study doctor may be required to report certain cases of abuse, neglect, or suicidal or homicidal intent to the appropriate authorities.

If as part of this study you tell study staff that you plan to hurt yourself or someone else you should know what would happen. We will refer you for an evaluation by a mental health professional. You should also know the study doctor may have to report it to the authorities. There is a chance the authorities and the mental health professionals will find out that you are participating in this study.

DATA MANAGEMENT:

All protocols at the NIA follow the NIA Data and Safety Monitoring Plan. This includes using the Level of Risk Assessment Monitoring Guidelines that has been established for the NIA following NIH rules and regulations to ensure good clinical practices in the conduct of clinical research. Participants will be informed about new information from this or other studies that may affect their health, welfare, or willingness to stay in this study.

Data collected from the HANDLS study including Personal Health Information (PHI) is stored in the secure databases located on the *handlsdb*, *handlsmrv* and *vhandlsdev* servers. These databases are password protected and maintained on a secure NIA/NIH system with access limited to authorized NIA staff. All NIA staff that has access to these databases has the proper training on patient confidentiality as well as the required Human Subject Protection training.

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The system is administered using the security policies and regulations required by the National Institutes of Health consistent with the Health and Human Services Privacy Rule and HIPAA. Organizations that may request inspect and/or copy research and medical records for quality assurance and data analysis include the National Institute on Aging, Office of Human Research Protection, and MedStar Health Research Institute, Institutional Review Board (IRB).

You can stop participating at any time. Any data or blood collected until that point in time would remain part of the study and the property of the National Institute on Aging. All data and blood collected is available only to authorized staff working on this protocol.

WILL I BE PAID FOR PARTICIPATING IN THIS STUDY?

The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines. Compensation of \$600 or more in one year will be reported to the IRS per federal regulations.

You will receive \$160 for the first phase (MRV visit) of the study. Your payment will be made in the form of an ATM debit card at the end of the MRV visit. If you are unable to complete all of the tests you may receive a portion of the payment. If you have to return to the MRVs to complete testing on another day, you could be compensated for the additional visit. The ATM card will be activated before you leave the vehicle. You will be able to take the card to an ATM machine in your neighborhood to withdraw your payment.

If you decide to participate in the second phase of this study, the follow-up telephone interview, scheduled to occur with-in 7-10 days of our MRV visit, you will be paid an additional \$40.00. Your payment will be added to the ATM debit card given to you during your MRV visit.

We will provide round-trip transportation from your home to our mobile testing center if you want it. We will serve a box breakfast and box lunch if you are participating in tests during mid-day. We will do our best to meet your dietary needs if you have any.

Materials and information obtained from you in this research may be used for commercial or non-commercial purposes. It is the policy of the National Institute on Aging, National Institutes of Health and affiliated entities not to provide financial compensation to you should this occur.

WHAT ARE THE COSTS?

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IRB number:	2009-149	2 Clinical S	ite Version: 08	3/01/2011
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Principal Inves	tigator:	Michele K. Evans, MD	Institution:	National Institute on Aging, NIH

You do not have to pay anything to be in this study. However, if taking part in this study leads to procedures or care not included in the study, it may lead to added costs for you or your insurance company. You will not be charged for tests that are part of this research study.

WHAT IF I'M INJURED OR BECOME ILL DURING THE STUDY?

We will make every effort to prevent injuries or illness from occurring while you are in study. In case of an injury, illness, or other harm occurring to you during or resulting directly from the study, the National Institute on Aging will provide short-term medical care for any injury resulting from your participation in research at the National Institute on Aging to the extent that such costs are not covered by your medical or hospital insurance.

You should contact the study doctor as soon as possible. The services at the National Institute on Aging will be open to you in case of any such injury. Emergency medical treatment is available, but you or your insurance will be charged for any continuing medical care or hospitalization that is provided at the usual charge by the Harbor Hospital and will not be reimbursed by the National Institute on Aging to the extent these costs are not covered by your insurance or other third party coverage.

No funds have been set aside by the National Institute on Aging, Harbor Hospital, the MedStar Health Research Institute, MedStar Health, or other affiliated entities to repay you in case of injury, illness, or other harm occurring during, or resulting from the study, and their current policies do not provide for payments for lost wages, cost of pain and suffering, or additional expenses. By agreeing to this information regarding injury or illness, you do not give up your rights to seek compensation in the courts.

WHAT CONSULTATIVE OR FINANCIAL INTERESTS ARE INVOLVED IN THIS STUDY?

The National Institutes of Health reviews NIH staff researchers at least yearly for conflicts of interest. The Following link contains details of this process http://ethics.od.nih.gov/forms/Protocol-Review-Guide.pdf. You may ask your research team for additional information or a copy of the Protocol Review Guide. This protocol may have investigators who are not NIH employees. Non-NIH investigators are expected to adhere to the principles of the Protocol Review Guide but are not required to report their personal financial holdings to the NIH.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

- You have the right to be told about the nature and purpose of the study;
- You have the right to be given an explanation of exactly what will be done in the study and given a description
 of potential risks, discomforts, or benefits that can reasonably be expected;

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- You have the right to be informed of any appropriate alternatives to the study, including, if appropriate, any drugs or devices that might help you, along with their potential risks, discomforts and benefits;
- You have the right to ask any questions you may have about the study;
- You have the right to decide whether or not to be in the study without anyone misleading or deceiving you; and
- You have the right to receive a copy of this consent form.

By signing this form, you will not give up any legal rights you may have as a research participant. You may choose not to take part in or leave the study at any time. If you choose to not take part in or to leave the study, your regular care will not be affected and you will not lose any of the benefits you would have received normally. We will tell you about new information that may affect your health, welfare, or willingness to be in this study.

WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the investigator, Michele K. Evans, MD at 410-558-8573. For medical assistance during the evening or on weekends, call the NIA Security Office at (410) 558-8119 and request that they contact the NIA Physician-on-Call.

If you are having a medical emergency, you should call 911 or go directly to the nearest emergency room.

If you are injured as a result of being in a study, or think you have not been treated fairly, please contact the NIA Clinical Director at (410) 350-3922.

For questions about your rights as a research participant, you can call or write the following:

NIA Clinical Director 3001 S. Hanover Street, 5th Floor Baltimore, MD 21225 Phone (410) 350-3922

NIA Clinical Research Protocol Office 3001 S. Hanover Street, Room 539 Baltimore, MD 21225 Telephone: (410) 350-3922 Fax: (410) 350-3979

Telephone: (410) 350-3947 Fax: (301) 451-5576

MedStar Health Research Institute Office of Research Integrity 6525 Belcrest Road, Suite 700 Hyattsville, MD 20782 Telephone: (301) 560-2912Toll Free: (800) 793-7175Fax: (301) 560-7336

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Principal Inves	stigator:	Michele K. Evans, MD	Institution:	National Institute on Aging, NIH

SIGNATURES

As a representative of this study, I have explained the purpose, the procedures, the possible benefits and risks that are involved in this research study. Any questions that have been raised have been answered to the individual's satisfaction.

Signature of Person Ob	taining Consent
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Print Name of Person Obtaining Consent

I, the undersigned have been informed about this study's purpose, procedures, possible benefits and risks, and I have received a copy of this consent. I have been given the opportunity to ask questions before I sign, and I have been told that I can ask other questions at any time. I voluntarily agree to be in this study. I am free to stop being in the study at any time without need to justify my decision and if I stop being in the study I understand it will not in any way affect my future treatment or medical management. I agree to cooperate with **Dr. Michele K. Evans** and the research staff and to tell them immediately if I experience any unexpected or unusual symptoms.

	Date of
Participant's Signature	Signature
Print Name of Participant	
	Date of
Signature of Witness	Signature
Print Name of Witness	
	the there reviewed this individual's eligibility
As the Principal Investigator (or his designee) for this research for enrollment in the study and agree that the individual is elig	gible to be enrolled.

MedStar Health Research Institute	Consent To Participate In A Medstar Health Research Institute Clinical Research Study	Mod Stato He all Approval Statinge APPROVAL DATE SEP 277112 APPROVAL EXPIRES SEP 262013
	Page 15 of 15	IRB APPROVED
	Participant Initial	Form Revision Date: 05/10/04

Date of Signature

APPENDIX F

INFORMED CONSENT FOR WAVE 3 HANDLS (FIRST FOLLOW-UP EXAMINATION)

MedStar Research Institute

Informed Consent for Clinical Research – HANDLS Phase 1

SITE: Mobile Medical Research Vehicles (MRVs) – 13 neighborhoods in Baltimore City

PRINCIPAL INVESTIGATOR: Michele K. Evans, M.D. & Alan B. Zonderman, Ph.D.

Co-INVESTIGATORS: D.R. Abernethy, D. Arking, M. Brock, N. Ejiogu, C. Fletcher, M.C. Gibbons, M.H. Kitner-Triolo, M.T. Fanelli Kuczmarski, T.A. LaVeist, J. Lepkowski, S. Ling, E. Nagababu, S. Najjar, N.R. Powe, J.M.Rifkind, A. Trzeciak,

INTRODUCTION

We invite you to take part in an observational research study called Healthy Aging in Neighborhoods of Diversity across the Life Span. You were selected as a possible participant in this study because we are looking for residents from your neighborhood between the ages of 30 and 64 years old. Please take your time to read this form, ask any questions you may have and make your decision. We encourage you to discuss your decision with your family and friends.

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to learn about changes in health over time. We want to study as many people in different neighborhoods as we can. Our goal is to study health change as people grow older. We plan to do this by studying the same people over many years. This gives us the information we want about how peoples' bodies change over time. We also want to study why some people are healthier than others as they get older. We want to discover if we can predict the causes of good health with aging. If we can find the causes of good health, then we might find the cures for some of the diseases related to aging. This is an observational study where we will follow you over the next twenty years to see how you age. This will help us learn about the natural course of diseases like heart disease, Alzheimer's disease, hypertension, diabetes and stroke. We are trying to understand why some Americans have higher rates of certain diseases and more severe diseases than other Americans. This research is being done so that we can discover better ways to prevent and treat disease.

WHAT ELSE SHOULD I KNOW ABOUT THIS RESEARCH STUDY?

It is important that you read and understand several points that apply to all who take part in our studies:

- Taking part in the study is entirely voluntary and refusal to participate will not affect any rights or benefits you normally have;
- You may or may not benefit from taking part in the study, but knowledge may be gained from your participation that may help others; and
- You may stop being in the study at any time without any penalty or losing any of the benefits you would have normally received.



Consent To Participate In A MedStar Research Institute Clinical Research Study

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IBB number:	2003-314	4	05	5/20/2008
Project Title:	Healthy	Aging in Neighborhoods of D	iversity acros	s the Life Span
Principal Inves	stigator:	MK Evans & AB Zonderman	Institution:	National Institute on Aging, NIH

The nature of the study, the benefits, risks, discomforts and other information about the study are discussed further below. If any new information is learned, at any time during the research, which might affect your participation in the study, we will tell you. We urge you to ask any questions you have about this study with the staff members who explain it to you and with your own advisors before agreeing to participate.

WHO IS IN CHARGE OF THIS STUDY?

The research is being conducted and sponsored by the National Institute on Aging with Michele K. Evans, M.D. and Alan B. Zonderman, Ph.D. as the primary investigators.

WHO CANNOT PARTICIPATE IN THIS STUDY?

You cannot be in this study if any of the following apply to you;

If you:

- Do not have a valid picture ID
- Are unable to give informed consent
- Are under 30 years old
- Are older than 64 years old
- Are pregnant
- Are currently undergoing cancer treatment (chemotherapy or radiation)
- Have undergone cancer treatment (chemotherapy or radiation) within the last 6 months

WHAT IF I AM PRESENTLY PARTICIPATING IN ANOTHER RESEARCH STUDY?

Are you presently participating in any other research studies? Yes 🗌 No 🗌

If yes, please state which study(ies):

While participating in this study, you should not take part in any other research project without approval from the people in charge of each study. This is to protect you from possible injury arising from such things as extra blood drawing, extra x-rays, interaction of research drugs, or similar hazards.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 4000 people will take part in this study, around 335 from your neighborhood.

WHAT HAPPENS IF I AGREE TO BE IN THE STUDY?

The study data will be collected in two parts. This is a consent form for the first part. You are required to give your consent for both parts.

This first part of the study consists of a household interview. This interview includes questions about your age, occupation, and neighborhood. We also want to know about your physical activities, use of dental and health services,

MedStar Research Institute	Consent To Participate In A MedStar Research Institute Clinical Research Study Page 2 of 7	IRB Approval Stamp (ORP USE ONLY - DO NOT CHANGE ANY INFORMATION IN THIS SECTION) MedStar Research Institute APPROVAL DATE JUN 24 2008 APPROVAL EXPIRES JUN 23 2009
	Participant Initial	Form Revision Date: 05/10/04

IRB number:	2003-314	1	05	5/20/2008
Project Title:	Healthy	Aging in Neighborhoods of D	iversity acros	s the Life Span
Principal Inves	tigator:	MK Evans & AB Zonderman	Institution:	National Institute on Aging, NIH

and stress that you might experience and how you deal with it. We will also ask you to remember all of the food that you ate in the past day. We will discuss the way the household interview will be conducted below.

In the second part of the study, you will spend a day at our Mobile Medical Research Vehicles (MRVs). While you are there, we will ask you for additional information and we will do additional tests. You will be asked about your medical history and you will receive a physical examination. We will ask what you ate during the last 24 hours. You will receive memory testing. We will also measure your emotions and heart rate changes, muscle strength, bone density and test for hardening of the arteries. We will also take blood, tissue and urine samples. You will be offered a test for HIV. If you decide to have the test, you will be asked to sign a separate consent form that explains the HIV testing procedures for the HANDLS study. You will also be asked to give a DNA sample by using a method called Buccal Mucosa smear. Before you agree to give the DNA sample you will be required to sign a separate consent that explains the procedures and risks of providing DNA samples. More details about the tests for the second part of the study are described in the attached **Consent Form Booklet**.

This first part of the study will take place in your home. We will ask you to answer questions about you and your physical activity, use of dental and health services, stress and how you deal with it and a few questions about your neighborhood. We will also ask you to complete a dietary recall questionnaire that asks you to remember what you had to eat and drink in the last 24 hours. We will use pictures to help you give us information about how much food and drink you had in the last 24 hours. We expect this household interview to take about 90 minutes.

All of the questionnaires collect information about our research. They are not designed to improve your health at this time. We perform these questionnaires free of charge. You may participate in both of the questionnaires, but you do not have to. You may stop any questionnaire after it starts. This will not affect your right to participate in this study. This is a longitudinal study. Our Mobile Medical Research Vehicles will return to your neighborhood every three years and we will ask you again at that time to participate in this study.

HOW LONG WILL I BE IN THE STUDY?

We think you will be in the study for the next 20 years because this is a longitudinal study that follows your health over time as you age. This is a study that provides long-term follow up. The study doctor or the National Institute on Aging may stop your participation in this study at any time without your consent. Any information (data) or blood collected until that point in time would remain part of the study. You can stop participating at any time. However, if you decide to stop participating in the study, we ask you to talk to the researchers first.

WHAT ARE THE RISKS AND SIDE EFFECTS OF THIS STUDY?

If you decide to participate in this study, you should know there may be risks. The risks for this study are minimal. The descriptions of the tests given on the Mobile Medical Research Vehicles include any risks and other possible side effects. They are also explained in the **Consent Booklet** under the Assessment of Risks section. For more information about risks and side effects, you should call the Principal Investigator, Michele K. Evans, M.D. at 410-558-8573.

As part of this study, you will be asked to sign a separate consent form to be in the part of this study involving genetic testing. Risks of genetic testing include the misuse of personal, genetic information. Although rare, misuse of such information has caused problems for persons related to employment, life, or health insurance benefits and right. There is a risk that being in a genetics study can cause psychological distress or tension with other family members. Although

MedStar Research Institute	Consent To Participate In A MedStar Research Institute Clinical Research Study Page 3 of 7	IRB Approval Stamp (ORP USE ONLY - DO NOT CHANGE ANY INFORMATION IN THIS SECTION) MedStar Research Institute APPROVAL DATE <u>JUN 24 2008</u> APPROVAL EXPIRES JUN 23 2009
	Participant Initial	IRB APPROVED Form Revision Date: 05/10/04

IRB number:	2003-314	1	05	5/20/2008
Project Title:	Healthy	Aging in Neighborhoods of D	iversity acros	s the Life Span
Principal Inves	stigator:	MK Evans & AB Zonderman	Institution:	National Institute on Aging, NIH

there can be no absolute guarantees, every reasonable effort will be made to keep your personally identifiable information secret so that there will be no misuse. Even when the information is kept secret, if you are asked if you have ever been tested for a genetic disorder, answering "yes" could cause benefits to be denied or could cause other problems including discrimination.

ARE THERE ANY BENEFITS TO TAKING PART IN THE STUDY?

This study is not designed to provide direct benefits to any participants. If you agree to take part in this study, there may or may not be direct medical benefits to you. We hope the information learned from this study will benefit others in the future. There is no charge for any of the testing described. You may benefit by learning more about your health, or possibly from learning that you have a condition or problem. You will receive a Participant Report Package in the mail, with results of your visit to the MRVs. If the study doctor discovers any condition or problem, the information will be provided to you and your doctor, if you authorize it. To authorize the reporting of results to your physician you will need to sign a form called "Release of Medical Information". You will be asked to sign this form only if you want us to communicate with your physician. The study doctors do not provide medical treatment. The information gained from this research may benefit others in the future.

WHAT OTHER OPTIONS ARE THERE?

There are no other options associated with your participation in this study. You may choose either to participate or not to participate in this research. Taking part in this study is entirely voluntary. You may choose to withdraw from the study at any time.

WHAT ABOUT CONFIDENTIALITY?

Your personal health information (PHI) will be kept private to the extent allowed by law. You will not be identified by name in any publications resulting from this study. You will be asked to sign a separate form that will give permission to the investigator, the sponsor, and certain other people, agencies or entities to look at and review the records related to this study including your personal health information and the information discovered during this study. If you do not wish to sign this permission form you will not be allowed to participate in this study.

Personal Health Information (PHI) is stored in secure databases. These databases are password protected and maintained on a secure NIA/NIH system with access limited to authorized NIA staff. All NIA staff that has access to these databases has the proper training on patient confidentiality as well as the required Human Subject Protection Training. The system is administered using the security policies and regulations required by the National Institutes of Health consistent with the Health and Human Services Privacy Rule and HIPAA.

Organizations that may request, inspect and/or copy your research and medical records for quality assurance and data analysis include groups such as: the National Institute on Aging, Office of Human Research Protection, MedStar Research Institute, Institutional Review Board (IRB), Coda and Westat.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this certificate the researchers cannot be forced to disclose information that may identify you, even by court subpoena, in any federal, state, or local civil, criminal, administrative, legislative or other proceedings. The researchers will use the certificate to resist any demands for information that would identify you, except as explained below.

MedStar Research Institute Consent To Participate In A MedStar Research Institute Clinical Research Study

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Participant Initial ___

IRB number:2003-31405/20/2008Project Title:Healthy Aging in Neighborhoods of Diversity across the Life SpanPrincipal Investigator:MK Evans & AB ZondermanInstitution:National Institute on Aging, NIH

The Certificate cannot be used to resist a demand for information from personnel of the U.S. Department of Health and Human Services that is used for auditing or program evaluation or for information that must be disclosed in order to meet federal regulations.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researcher may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent researcher from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following conditions: It does not apply to state requirements to report certain communicable diseases. In addition, the study doctor may be required to report certain cases of abuse, neglect, or suicidal or homicidal intent to the appropriate authorities.

WILL I BE PAID FOR PARTICIPATING IN THIS STUDY?

You may be paid up to \$150 for your study visit. If you are unable to complete all the tests you may receive a portion of that payment. You will receive your payment in the form of an ATM debit card at the end of the MRV visit. The ATM card will be activated before you leave the vehicle. You will be able to take the card to an ATM machine in your neighborhood to withdraw your payment. We will provide round-trip transportation from your home to our mobile testing center if you want it. We will serve a box breakfast and box lunch if you are participating in tests during mid-day. We will do our best to meet your dietary needs if you have any.

WHAT ARE THE COSTS?

You do not have to pay anything to be in this study. However, if taking part in this study leads to procedures or care not included in the study, it may lead to added costs for you or your insurance company. You will not be charged for any tests or procedures that are part of this research study.

WHAT IF I'M INJURED OR BECOME ILL DURING THE STUDY?

We will make every effort to prevent injuries and illness from being in the study. If you have any adverse experience resulting directly from the study, the National Institute on Aging *will* provide or pay for short-term medical care for any injury resulting from participation in research here as long as the costs are not covered by your medical or hospital insurance. You should not expect any one to pay you for pain, worry, lost income, or non-medical care costs that occur from taking part in this research study. No other form of compensation is available for any adverse experience. *The National Institute on Aging, National Institutes of Health, the Federal Government, the MedStar Research Institute, MedStar Health, CODA or Westat* do not have money set aside to repay you in case of injury.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

You have the right to be told about the nature and purpose of the study; You have the right to be given an explanation of the exactly what will be done in the study and given a description of potential risks, discomforts, or benefits that can reasonably be expected;

MedStar Research Institute Consent To Participate In A MedStar Research Institute Clinical Research Study

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Participant Initial _

IRB number: 2003-314 Project Title: Healthy Aging in Neighborhoods of Diversity across the Life Span Principal Investigator: MK Evans & AB Zonderman Institution: National Institute on Aging, NIH

You have the right to be informed of any appropriate alternatives to the study, including, if appropriate, any drugs or devices that might help you, along with their potential risks, discomforts and benefits;

You have the right to ask any questions you may have about the study;

You have the right to decide whether or not to be in the study without anyone misleading or deceiving you; and You have the right to receive a copy of this consent form.

By signing this form, you will not give up any legal rights you may have as a research participant. You may choose not to take part in or leave the study at any time. If you choose to not take part in or to leave the study, you will not lose any of the benefits you would have received normally. We will tell you about new information that may affect your health, welfare, or willingness to be in this study.

WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the investigator, Michele K. Evans, M.D., at (410)-558-8573. For medical assistance during the evening or on weekends, call the NIA Security Office at (410) 558-8119 and request that they contact the NIA Physician-on-Call.

If you are having a medical emergency, you should call 911 or go directly to the nearest emergency room.

If you are injured as a result of being in a study, or think you have not been treated fairly, please contact the NIA Clinical Director or Deputy Clinical Director at (410) 350-3922.

For questions about your rights as a research participant, you can call or write the following:

NIA Clinical Director 3001 S. Hanover Street, 5th Floor Baltimore, MD 21225 Phone (410) 350-3922

NIA Clinical Research Protocol Office 3001 S. Hanover Street, Room 539 Baltimore, MD 21225 Phone: (410) 350-3947 Fax: (410) 350-3979.

MedStar Research Institute Office of Research Integrity 6495 New Hampshire Avenue, Suite 201 Hyattsville, MD 20783 Phone: (301) 560-7339 Toll Free: (800) 793-7175 Fax: (301) 560-7336

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Consent To Participate In A MedStar Research Institute Clinical Research Study

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Principal Inves	tigator:	MK Evans & AB Zonderman	Institution:	National Institute on Aging, NIH	

SIGNATURES

As a representative of this study, I have explained the purpose, the procedures, the possible benefits and risks that are involved in this research study. Any questions that have been raised have been answered to the individual's satisfaction.

Date of Signature

Signature of Person Obtaining Consent

I, the undersigned have been informed about this study's purpose, procedures, possible benefits and risks, and I have received a copy of this consent. I have been given the opportunity to ask questions before I sign, and I have been told that I can ask other questions at any time. I voluntarily agree to be in this study. I am free to stop being in the study at any time without need to justify my decision and if I stop being in the study I understand it will not in any way affect my future treatment or medical management. I agree to cooperate with Dr. Michele K. Evans, Dr. Alan B. Zonderman, and the research staff and to tell them immediately if I experience any unexpected or unusual symptoms.

Participant's Signature	Date of Signature
Signature of Witness	Date of Signature
Signature of Legally Authorized Representative (When Appropriate)	Date of Signature
Relationship to Participant (When Appropriate)	Date of Signature



 IRB number:
 2003-314
 Clinical Site IC Version: 05/20/2008

 Project Title:
 Healthy Aging in Neighborhoods of Diversity across the Life Span

 Principal Investigator:
 MK Evans & AB Zonderman
 Institution:
 National Institute on Aging, NIH

MedStar Research Institute

Informed Consent for Clinical Research – HANDLS Phase 2

SITE: Mobile Medical Research Vehicles (MRVs) -- 13 neighborhoods in Baltimore City

PRINCIPAL INVESTIGATOR: Michele K. Evans, M.D. & Alan B. Zonderman, Ph.D.

CO-INVESTIGATORS: D.R. Abernethy, D. Arking, M. Brock, N. Ejiogu, C. Fletcher, M.C. Gibbons, M.H. Kitner-Triolo, M.T. Fanelli Kuczmarski, T.A. LaVeist, J. Lepkowski, S. Ling, E. Nagababu, S. Najjar, N.R. Powe, J.M.Rifkind, A. Trzeciak

INTRODUCTION

We invite you to take part in an observational research study called Healthy Aging in Neighborhoods of Diversity across the Life Span. You were selected as a possible participant in this study because we are looking for residents from your neighborhood between the ages of 30 and 64 years old. Please take your time to read this form, ask any questions you may have and make your decision. We encourage you to discuss your decision with your family and friends.

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to learn about changes in health over time. We want to study as many people in different neighborhoods as we can. Our goal is to study health change as people grow older. We plan to do this by studying the same people over many years. This gives us the information we want about how peoples' bodies change over time. We also want to study why some people are healthier than others as they get older. We want to discover if we can predict the causes of good health with aging. If we can find the causes of good health, then we might find the cures for some of the diseases related to aging. This is an observational study where we will follow you over the next twenty years to see how you age. This will help us learn about the natural course of diseases like heart disease, Alzheimer's disease, hypertension, diabetes and stroke. We are trying to understand why some Americans have higher rates of certain diseases and more severe diseases than other Americans. This research is being done so that we can discover better ways to prevent and treat disease.

WHAT ELSE SHOULD I KNOW ABOUT THIS RESEARCH STUDY?

It is important that you read and understand several points that apply to all who take part in our studies:

- Taking part in the study is entirely voluntary and refusal to participate will not affect any rights or benefits you normally have;
- You may or may not benefit from taking part in the study, but knowledge may be gained from your participation that may help others; and
- You may stop being in the study at any time without any penalty or losing any of the benefits you would have normally received.

The nature of the study, the benefits, risks, discomforts and other information about the study are discussed further below. If any new information is learned, at any time during the research, which might affect your participation in the

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Principal Inves	tigator:	MK Evans & AB Zonderman	Institution:	National Institute on Aging, NIH

study, we will tell you. We urge you to ask any questions you have about this study with the staff members who explain it to you and with your own advisors before agreeing to participate.

WHO IS IN CHARGE OF THIS STUDY?

The research is being conducted and sponsored by the National Institute on Aging with Michele K. Evans, M.D. and Alan B. Zonderman, Ph.D. as the primary investigators.

WHO CANNOT PARTICIPATE IN THIS STUDY?

You cannot be in this study if any of the following apply to you;

If you:

_

- Do not have a valid picture ID
- Are unable to give informed consent
- Are under 30 years old
- Are older than 64 years old
- Are pregnant
- Are currently undergoing cancer treatment (chemotherapy or radiation)
- Have undergone cancer treatment (chemotherapy or radiation) within the last 6 months

WHAT IF I AM PRESENTLY PARTICIPATING IN ANOTHER RESEARCH STUDY?

Are you presently participating in any other research studies? Yes No

If yes, please state which study(ies):

While participating in this study, you should not take part in any other research project without approval from the people in charge of each study. This is to protect you from possible injury arising from such things as extra blood drawing, extra x-rays, interaction of research drugs, or similar hazards.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 4000 people will take part in this study, around 335 from your neighborhood.

WHAT HAPPENS IF I AGREE TO BE IN THE STUDY?

The study data will be collected in two parts. This is a consent form for the second part. You are required to give your consent for both parts. The first part of the study included a household interview with questions about your age, occupation and neighborhood. We asked about your physical activity, use of dental and health services, and stress you may have experienced. We also asked you to complete a dietary recall questionnaire during the home visit.

This second part of the study will require you to spend a day at our Mobile Medical Research Vehicles (MRVs) to have testing. You will be asked about your medical history and you will receive a physical examination. We will ask you to remember all of the food you ate in the last day. We will measure your emotions and heart rate changes, muscle

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Project Title: Principal Inves	tigator: MK Evans & AB Zonderman Inst	itution: National Institute on Aging, NIH

strength, bone density and you will have a test for hardening of the arteries. We will also take blood, tissue and urine samples. You will be offered a test for HIV. If you decide to have the test, you will be asked to sign a separate consent form that explains the HIV testing procedures for the HANDLS study. You will also be asked to give a DNA sample by using a method called Buccal Mucosa smear. Before you agree to give the DNA sample you will be required to sign a separate consent that explains the procedures and risks of providing DNA samples. More details about the specific testing for this part of the study are described below and in the attached **Consent Booklet**.

The tests involved in this study are described in the attached **Consent Booklet**. All of the tests are performed for the purpose of research and are not designed to improve your health at this time. There are no experimental tests or procedures in this study. We perform these tests free of charge. If, after reading the **Consent Booklet**, there are tests in which you do not wish to participate, please list them on the back of this form.

Below is a chart that shows the tests you will be expected to complete. This chart also tells you how long we think it will take each test to be done and in which vehicle it will be given. You will find more details about each test in the **Consent Booklet** that goes with this form.

Procedure	Where	Expected	Maximum Time
			60 minutes
Tests of Heart Function:	MRV 1	50 minutes	
Carotid Doppler			
Ultrasonography, Pulse Wave			
Velocity, and EKG			25 minutos
Bone Density and Body	MRV I	30 minutes	35 minutes
Composition Tests:			
DEXA Scanner, Weight and Body			
Measurements			
			15 minutos
Muscle Strength Function	MRV I	10 minutes	15 minutes
Testing: Grip Strength, Chair			
Stand, and Balance Tests			45
Blood, Tissue and Urine	MRV I	10 minutes	15 minutes
Sampling			
Medical History & Physical	MRV I	50 minutes	60 minutes
Examination			
Nutritional Dietary Recall	MRV I	20 minutes	30 minutes
Emotions and Heart Rate Testing	MRV II	45 minutes	55 minutes
Problem Solving and Memory	MRV II	50 minutes	60 minutes
Testing			
Audio-administered	MRV II	20 minutes	30 minutes
Ouestionnaire			



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 Healthy Aging in Neighborhoods of Diversity across the Life Span

 Principal Investigator:
 MK Evans & AB Zonderman
 Institution:
 National Institute on Aging, NIH

You may participate in any of the tests, but you do not have to participate in all of the tests. This will not affect your right to participate in this study. You may stop any test after it starts. If you are unable to complete all of the tests in one visit you may be invited to return to the MRVs to complete your testing.

This is a long-term study, our Mobile Medical Research Vehicles will be back in your neighborhood every three years and we will ask you again at that time to participate in this study.

HOW LONG WILL I BE IN THE STUDY?

We think you will be in the study for the next 20 years because this is a longitudinal study that follows your health over time as you age. This is a study that provides long-term follow up. The study doctor or the National Institute on Aging may stop your participation in this study at any time without your consent. Any information (data) or blood collected until that point in time would remain part of the study. You can stop participating at any time. However, if you decide to stop participating in the study, we ask you to talk to the researchers first.

WHAT ARE THE RISKS AND SIDE EFFECTS OF THIS STUDY?

If you decide to participate in this study, you should know there may be risks. The risks for this study are minimal. The descriptions of the tests given on the Mobile Medical Research Vehicles include any risks and other possible side effects. They are also explained in the **Consent Booklet** under the Assessment of Risks section.

This research study requires a small amount of radiation from the DEXA Scans. It must be noted that this radiation exposure is **not** needed for your medical care and is for research purposes only. The total amount of radiation you will receive from this study is from four DEXA scans: the whole body, spine,hip and a scan called the Instant Vertebral Assessment (IVA) that allows for screening of vertebral fractures. 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 needed to obtain the research information desired.

Using the standard way of describing radiation exposure, from one DEXA Scan you will receive an effective dose of less than one thousandth of one rem. By comparison the average person in the United States receives this much radiation every day from natural sources, such as the sun. In this scan the only part of the body exposed is the skin, which is less sensitive to radiation than other parts of the body. There is a very small risk of cancer from the x-rays in DEXA scan, but is too small to measure.

If you are pregnant you may not participate in this study. Unborn babies are more sensitive to radiation than children or adults.

As part of this study, you will be asked to sign a separate consent form to be in the part of this study involving genetic testing. Risks of genetic testing include the misuse of personal, genetic information. Although rare, misuse of such information has caused problems for persons related to employment, life, or health insurance benefits and right. There is a risk that being in a genetics study can cause psychological distress or tension with other family members. Although there can be no absolute guarantees, every reasonable effort will be made to keep your personally identifiable information secret so that there will be no misuse. Even when the information is kept secret, if you are asked if you have ever been

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tested for a genetic disorder, answering "yes" could cause benefits to be denied or could cause other problems including discrimination.

For more information about risks and side effects, you should call the Principal Investigator, Michele K. Evans, M.D. at 410-558-8573.

ARE THERE ANY BENEFITS TO TAKING PART IN THE STUDY?

This study is not designed to provide direct benefits to any participants. If you agree to take part in this study, there may or may not be direct medical benefits to you. We hope the information learned from this study will benefit others in the future. There is no charge for any of the testing described. You may benefit by learning more about your health, or possibly from learning that you have a condition or problem. You will receive a Participant Report Package in the mail, with results of your visit to the MRVs. If the study doctor discovers any condition or problem, the information will be provided to you and your doctor, if you authorize it. To authorize the reporting of results to your physician you will need to sign a form called "Release of Medical Information". You will be asked to sign this form only if you want us to communicate with your physician. The study doctors do not provide medical treatment. The information gained from this research may benefit others in the future.

WHAT OTHER OPTIONS ARE THERE?

There are no other options associated with your participation in this study. You may choose either to participate or not to participate in this research. Taking part in this study is entirely voluntary. You may choose to withdraw from the study at any time.

WHAT ABOUT CONFIDENTIALITY?

Your personal health information (PHI) will be kept private to the extent allowed by law. You will not be identified by name in any publications resulting from this study. You will be asked to sign a separate form that will give permission to the investigator, the sponsor, and certain other people, agencies or entities to look at and review the records related to this study including your personal health information and the information discovered during this study. If you do not wish to sign this permission form you will not be allowed to participate in this study.

Personal Health Information (PHI) is stored in secure databases. These databases are password protected and maintained on a secure NIA/NIH system with access limited to authorized NIA staff. All NIA staff that has access to these databases has the proper training on patient confidentiality as well as the required Human Subject Protection Training. The system is administered using the security policies and regulations required by the National Institutes of Health consistent with the Health and Human Services Privacy Rule and HIPAA.

Organizations that may request inspect and/or copy your research and medical records for quality assurance and data analysis include groups such as: the National Institute on Aging, Office of Human Research Protection, MedStar Research Institute, Institutional Review Board (IRB), Coda and Westat.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this certificate the researchers cannot be forced to disclose information that may identify you, even by court

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IRB Approval Stamp (ORP USE ONLY - DO NOT CHANGE ANY INFORMATION IN THIS SECTION) MedStar Research Institute APPROVAL DATE <u>JUN 24 2008</u> APPROVAL EXPIRES JUN 23 2009 IRB APPROVED Form Revision Date: 05/1004

Participant Initial

IRB number:	2003-314	<u>4</u> Clinical S	Site IC Version: 05	5/20/2008	
Project Title:	Healthy Aging in Neighborhoods of Diversity across the Life Span				
Principal Inves	tigator:	MK Evans & AB Zonderma	an Institution:	National Institute on Aging, NIH	

subpoena, in any federal, state, or local civil, criminal, administrative, legislative or other proceedings. The researchers will use the certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the U.S. Department of Health and Human Services that is used for auditing or program evaluation or for information that must be disclosed in order to meet federal regulations.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researcher may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following conditions: It does not apply to state requirements to report certain communicable diseases. In addition, the study doctor may be required to report certain cases of abuse, neglect, or suicidal or homicidal intent to the appropriate authorities.

WILL I BE PAID FOR PARTICIPATING IN THIS STUDY?

You may be paid up to \$150 for your study visit. If you are unable to complete all of the tests you may receive a portion of that payment. You will receive your payment in the form of an ATM debit card at the end of the MRV visit. The ATM card will be activated before you leave the vehicle. You will be able to take the card to an ATM machine in your neighborhood to withdraw your payment. We will provide round-trip transportation from your home to our mobile testing center if you want it. We will serve a box breakfast and box lunch if you are participating in tests during mid-day. We will do our best to meet your dietary needs if you have any.

WHAT ARE THE COSTS?

You do not have to pay anything to be in this study. However, if taking part in this study leads to procedures or care not included in the study, it may lead to added costs for you or your insurance company. You will not be charged for any tests or procedures that are part of this research study.

WHAT IF I'M INJURED OR BECOME ILL DURING THE STUDY?

We will make every effort to prevent injuries and illness from being in the study. If you have any adverse experience resulting directly from the study, the National Institute on Aging *will* provide or pay for short-term medical care for any injury resulting from participation in research here as long as the costs are not covered by your medical or hospital insurance. You should not expect any one to pay you for pain, worry, lost income, or non-medical care costs that occur from taking part in this research study. No other form of compensation is available for any adverse experience. *The National Institute on Aging, National Institutes of Health, the Federal Government, the MedStar Research Institute, MedStar Health, CODA or Westat* do not have money set aside to repay you in case of injury.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

You have the right to be told about the nature and purpose of the study;



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Participant Initial

IRB number:	2003-314 Clinical Site IC Versi		IC Version: 05	rsion: 05/20/2008 ty across the Life Span	
Project little:	nearmy	Aging in Neighborhoods of E	iversity deree	At the theory Anima All I	
Principal Invest	tigator:	MK Evans & AB Zonderman	Institution:	National Institute on Aging, NIT	

You have the right to be given an explanation of the exactly what will be done in the study and given a description of potential risks, discomforts, or benefits that can reasonably be expected;

You have the right to be informed of any appropriate alternatives to the study, including, if appropriate, any drugs or devices that might help you, along with their potential risks, discomforts and benefits;

You have the right to ask any questions you may have about the study;

You have the right to decide whether or not to be in the study without anyone misleading or deceiving you; and You have the right to receive a copy of this consent form.

By signing this form, you will not give up any legal rights you may have as a research participant. You may choose not to take part in or leave the study at any time. If you choose to not take part in or to leave the study, you will not lose any of the benefits you would have received normally. We will tell you about new information that may affect your health, welfare, or willingness to be in this study.

WHO DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the investigator, Michele K. Evans, M.D., at (410)-558-8573. For medical assistance during the evening or on weekends, call the NIA Security Office at (410) 558-8119 and request that they contact the NIA Physician-on-Call.

If you are having a medical emergency, you should call 911 or go directly to the nearest emergency room.

If you are injured as a result of being in a study, or think you have not been treated fairly, please contact the NIA Clinical Director or Deputy Clinical Director at (410) 350-3922.

For questions about your rights as a research participant, you can call or write the following:

NIA Clinical Director 3001 S. Hanover Street, 5th Floor Baltimore, MD 21225 Phone (410) 350-3922

NIA Clinical Research Protocol Office 3001 S. Hanover Street, Room 539 Baltimore, MD 21225 Phone: (410) 350-3947 Fax: (410) 350-3979.

MedStar Research Institute Office of Research Integrity 6495 New Hampshire Avenue, Suite 201 Hyattsville, MD 20783 Phone: (301) 560-7339 Toll Free: (800) 793-7175 Fax: (301) 560-7336

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Principal Inves	tigator:	MK Evans & AB Zonderman	Institution:	National Institute on Aging, Nin		

SIGNATURES

As a representative of this study, I have explained the purpose, the procedures, the possible benefits and risks that are involved in this research study. Any questions that have been raised have been answered to the individual's satisfaction.

Date of Signature

Signature of Person Obtaining Consent

I, the undersigned have been informed about this study's purpose, procedures, possible benefits and risks, and I have received a copy of this consent. I have been given the opportunity to ask questions before I sign, and I have been told that I can ask other questions at any time. I voluntarily agree to be in this study. I am free to stop being in the study at any time without need to justify my decision and if I stop being in the study I understand it will not in any way affect my future treatment or medical management. I agree to cooperate with Dr. Michele K. Evans, Dr. Alan B. Zonderman, and the research staff and to tell them immediately if I experience any unexpected or unusual symptoms.

	Date of Signature
Participant's Signature	
Signature of Witness	Date of Signature
Scenture of Legally Authorized Representative (When Appropriate)	Date of Signature
Signature of Legany Automatic Representative (many propriety)	
	Date of Skinature
Relationship to Participant (When Appropriate)	

