OSTEOPOROSIS – EXPLORING CHARACTERISTICS AMONGST NON-HISPANIC BLACK WOMEN ASSOCIATED WITH LOW BONE MASS (OSTEPENIA) AND OSTEOPOROSIS, WHO ARE THUS MORE LIKELY TO SUFFER OSTEOPOROTIC INJURIES IN THE FUTURE

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Abstract

Title: OSTEOPOROSIS – EXPLORING CHARACTERISTICS AMONGST NON-HISPANIC BLACK WOMEN ASSOCIATED WITH LOW BONE MASS (OSTEPENIA) AND OSTEOPOROSIS, WHO ARE THUS MORE LIKELY TO SUFFER OSTEOPOROTIC INJURIES IN THE FUTURE

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Statement of the Problem: Non-Hispanic black women have higher bone mass and lower rates of osteoporosis; however, age-related bone loss occurs at rates equal to other races. Osteopenia or osteoporotic occurs at greater age for non-Hispanic black women and may increase their risk of poor outcomes post an osteoporotic injury. It is important to determine what clinical characteristics or assessment standards to use to predict who may be more likely to develop osteopenia or osteoporosis in this population.

Methods: A retrospective database analysis of NHANES 4-year survey cycle: 2007-208 and 2009-2010 to examine characteristics associated with low bone mass and osteoporosis in non-Hispanic black females aged 20 and older. Evaluation of standard bone mineral density (BMD) T-scores compared to mean referent value for young, healthy non-Hispanic black females BMD scores.

Results: A total of 190 (20.7%) non-Hispanic black females had osteopenia or osteoporosis compared to 770 (32.3%) non-Hispanic white females($p<.0001$). Among non-Hispanic black females, osteopenia and osteoporosis were associated with being aged 50 or older (ORadj = 2.8, $p=0.0003$), less than a high school education (ORadj = 1.6, $p=0.02$) and menopause (ORadj = 2.0, $p=0.0036$). Osteopenia or osteoporosis was less likely if obese (ORadj = 0.5,

p=0.003). Each increased year in age, total femur BMD declined 0.43 points (<.0001) and 0.38 points (<.0001) for spinal BMD. When the non-Hispanic black referent was used, 91 (9.9%) had BMD classifications that worsen to osteopenia or osteoporosis: they were older (p<.0001), menopausal (p<.001), not obese (p<.001), experienced a hip fracture (p<.0001), taking diabetes (p<.001) or cardiovascular medication (p<.01) or had a close relative with asthma (p<.001).

Conclusions: Calculation of BMD T-score using the referent mean value for young (20-29-year-olds), healthy non-Hispanic black females instead of the standard for non-Hispanic white females were more sensitive in detecting additional individuals with low bone mass (osteopenia) or osteoporosis. Use of the standardized BMD and FRAX may be of limited utility in distinguishing those within a low-risk population, who may be at greater risk. Use of a non-Hispanic black specific measure may lead to earlier detection and intervention in this population.

Acknowledgement

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Dedication

To my loving and supportive husband Brian who gave me the time and space to pursue this dream.

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Chapter I

Introduction

Osteoporosis is a disease where bones lose mass and become more porous over time. This loss of mass and structural integrity is linked to the occurrence of bone fractures. Osteoporosis is insidious as this loss of bone mass is asymptomatic. The majority of those with osteoporosis are unaware of their condition until they suffer an osteoporotic fracture. The global prevalence of osteoporosis is estimated to be 200 million women and men[1]. It is estimated in the United States over 53 million people over the age of 50 have either low bone mass or osteoporosis[2]. Women are afflicted by low bone mass and osteoporosis at a higher rates than men[2]. Osteoporosis is a major contributor to fractures particularly those fractures resulting from a minor traumatic injury with an estimated incidence of 9 million fractures due to osteoporosis worldwide in 2000[3]. Modeling by Burges *et al,* estimated over 2 million fractures within the US among those ≥50 years with projected costs of $17 billion in healthcare costs[4].

The diagnosis of osteoporosis is made through the measurement of bone mineral density (BMD). BMD is calculated as a T-score using the mean value of normal, healthy, non-Hispanic white females aged 20-29 as the referent group. Those with a BMD which is <-2.5 standard deviation from the reference is defined as osteoporosis. Low bone mass or osteopenia is defined as a T score between 1 and -2.5 standard deviations from the reference.

Background of the Problem

In the United States, the documented prevalence of osteoporosis among non-Hispanic black women is lower than rates among non-Hispanic white, Hispanic, and non-Hispanic Asians women[2]. Although the rates of osteoporosis among non-Hispanic black women are lower than rates seen in non-Hispanic white women, non-Hispanic black women are still susceptible to the development of osteoporosis and its negative effects (fracture and disability). Costs incurred from osteoporotic fracture were highest for non-Hispanic blacks compared to other racial group and are estimated to increase by 79% by 2025 over a twenty year period[4].

However, exact osteoporosis prevalence and incidence rates are only estimated as the disease remains significantly under diagnosed. It has been estimated that less of 30% of women who have osteoporosis actually receive a diagnosis as screening rates are low[5]. This is especially true for non-Hispanic black women for whom disparities in screening for osteoporosis have been documented[6]. In addition, to having lower screening rates, non-Hispanic black women once diagnosed, have lower rates of treatment then their non-Hispanic white counterparts[7]. Despite its public health significance, osteoporosis remains underdiagnosed and undertreated overall but particularly so in the Non-Hispanic black community.

Lower bone mass density (BMD) levels have been found to be associated with a higher risk of death from all causes in all race/ethnic groups and for males and females[8]. The lower prevalence of osteoporosis among non-Hispanic black men and women is believed to be due to differences in bone structure and a higher level of peak bone mass (highest amount of bone mass one accumulates) attainment[9]. Even with having on average higher bone mass and lower rate of osteoporosis, non-Hispanic black women are not immune from

losing bone mass as age-related declines in bone mass is consistent for all race/ethnic groups. Thus, Non-Hispanic black women are still susceptible to suffering osteoporotic fractures. Although non-Hispanic black women experience the occurrence of fractures at a lower rate than non-Hispanic white women regardless of age[10], they experience greater morbidity and mortality as a result of a fracture then do non-Hispanic white women[11,12].

Statement of the Problem

As Non-Hispanic black women have lower rates of osteoporosis, there is limited research focusing on this population. Starting with overall higher levels of peak bone mass by the age of 30, the rate of age-related bone loss may result in Non-Hispanic black women reaching low bone mass or osteoporotic levels at a greater age; therefore may increase the likelihood that Non-Hispanic black women would potentially suffer worse outcomes as a result of an osteoporotic injury compared to other racial groups. Given the lower estimated prevalence of osteoporosis among Non-Hispanic black women, it is important to determine what clinical characteristics could be used to predict those Non-Hispanic black women who would be more likely to develop osteoporosis or suffer a fracture due to osteoporosis compared to other Non-Hispanic black women. The primary goal of this dissertation is to identify characteristics that can identify Non-Hispanic black women who are at risk for suffering a future osteoporotic injury and to assess the possible use of a mean reference based-on healthy young non-Hispanic black females in calculating bone mineral density T-scores instead of the standard mean reference for young healthy non-Hispanic white females. The National Health and Nutrition Examination Survey (NHANES) database will be used in these analyses.

Hypotheses

1) Non-Hispanic black females will have lower levels of concordance between the perceptions of osteoporosis risk and BMD levels compared to non-Hispanic white women.
2) Use of normative reference value of young (aged 20-29-years), healthy in calculating T-scores for non-Hispanic black female participants will have more predictive value then the use of the standard reference value based on values from healthy normal young non-Hispanic White females.
3) Due to higher peak bone mass, non-Hispanic black females will develop osteopenia and osteoporosis at later ages than non-Hispanic white females.

Chapter II

Review of Related Literature

History of Osteoporosis

Evidence for the existence of osteoporosis has been document thorough the ages. Archeologists have discovered in Egyptian mummies from more than 4,000 years ago the that show the signs of osteoporotic changes[13]. Paleo pathologists have found evidence of osteoporosis in examination of bones from male and female skeletons[13]. Researchers found patterns of loss of bone mass similar to those seen today[13]: Both Neolithic male and female skeletons from 4,700 BC were found to have evidence of diminishment of cortical thickness[13] and Nubian skeletal remains indicated bone mass loss started when one was in their thirties[13].

The signs and symptoms of osteoporosis have been observed for centuries and had been assumed to be an unchangeable part of the normal aging process and not a disease state[14]. In the 18th century, John Hunter was one of the first to note that bones were not static but grew "…at the outer surface like a tree."[14]. Later scientists[14] would expand on his work leading to our understanding of bone formation and absorption. The condition was first described by Jean Georges Chretien Frederic Martin Lobstein, a French pathologist, in the 1820s[14]. He was the first to use the word 'osteoporosis meaning "porous bone" hole[14]. Lobstein; however, did not view the porous bones as indication of a disease state. In the early 19th century, Sir Astley Cooper was the first to associate 'age-related' bone loss with increase in fracture risk. It was not until the late 19th century that the medical community began to view osteoporotic changes as pathological.

During the late 1920s through the 1930s, researchers in the field of endocrinology studied the links between hormones and bone physiology. In research studying pigeons in 1934, Preston Kyes and Truman Potter observed changes in female bone formation which appeared to be linked to the female ovulation cycle. Estrogen was quickly founded to play a vital role in bone formation and resorption process[15].

Fuller Albright observed that osteoporotic bones were deficient in a certain type of bone cells called osteoblasts which therefore were not reforming bone sufficiently[16]. Particularly, this was observed in the spine, pelvis and 'long bones'[14]. These observations were found most commonly in the bones of post-menopausal women. As these earlier findings were primarily observed in women, osteoporosis was primarily thought to be a disease afflicting only women. Estrogen and testosterone were documented by Albright to have a positive effect in the treatment of postmenopausal osteoporosis[16].

Osteoporosis can be classified into two different types based on the cause of the osteoporosis: primary and secondary[17]. The major form of osteoporosis is the primary form and is related to aging and menopausal status[18]. Both men and women are affected by primary osteoporosis which accounts for more than 80% of osteoporosis among men and greater than 95% for women[17]. The cause of primary osteoporosis is related to lower estrogen and testosterone levels which naturally occurs with aging. Other causes of primary osteoporosis is related to deficiencies in calcium and vitamin D[17].

Secondary osteoporosis is caused as a result of particular medical conditions. Secondary osteoporosis accounts for less than five percent of osteoporosis cases diagnosed.

Table 1: Lists medical conditions can result in a reduction of bone mass and lead to osteoporosis (see Table 1).

List of Conditions and Medications Known to Cause Osteoporosis
Cancers

Chronic Kidney Disease
Chronic Pulmonary Obstructive Disorder
Endocrine disorders (e.g., hypogonadism, hyperparathyroidism, Cushing's syndrome, diabetes)
Hypercalcuria (excess urinary calcium excretion)
Excessive vitamin A levels (hypervitaminosis A)
Hypophosphatasia (results in low levels of alkaline phosphatase (ALP)
Immobilization
Liver disease
Malabsorption syndromes
Medications
Rheumatoid Arthritis

Source: Merck Manual

Overview of Bone Pathophysiology

There are 213 individual bones in the adult human body[19]. Bone is made of both an 'organic matrix' and mineral (mostly hydroxyapatite)[20,21]. The function of our skeleton is to provide protection to the organs and is the body's structural system. Movement would be impossible with the body's skeletal architectural structure. In addition to these important functions, our bones serve as the body's main 'storehouse' minerals and 'bone matrix proteins'[5]. The vast majority (99%) of the body's calcium (in the form of hydroxyapatitie[19] are reserved within the skeleton[5]. The other major minerals stored within the body's bones are phosphate (85%) and 50% of the body's magnesium storage[5].

Bone is made up of two types of tissues: Cortical or compact bone and trabecular or spongey bone[20]. Cortical bone tissue makes up to 80% of the body's "bone mineral mass"[20]. Cortical bone cells or osteons are known as Haversian systems[19]. Structurally cortical bone

resembles long concentric columns surrounding the Haversian canal (blood and lymphatic systems, nerves and connective tissues)[21].

Cortical bone forms the outer hard layer of most bones, particularly found in the "shafts of the long bones and outer surfaces of flat bones"[20] (Figure 1 shows areas of the skeleton that are majorly composed of cortical bone). Cortical bone can also be found surrounding trabecular bone at the bone joints. The strength of the cortical bone is proportional to the diameter size of the bone (greater diameter the stronger the bone)[14]. The strength of cortical bone diminshes as it becomes more porous which occurs as one ages[22].

Known as 'cancellous or spongy' bone[20] is the second type of bone tissue. The cranium, vertebral column, thorax and pelvis are primarily composed of trabecular bone[5]. The structure of trabecular bone resembles a lace-like lattice work of rods and plates[5,21,23]. Compared to cortical bone tissue, trabecular bone tissue is weaker in structure. This is due to trabecular bone undergoing a higher rate of metabolic changes compared to cortical bone[21]; thereby, making trabecular bone more susceptible to age-related bone loss, and as a result , it is at increased risk for low impact fracture compared to cortical bone[20]. (Figure 2 provides an illustration of bone structure.)

Figure 1: Bones primarily composed of cortical bone[24]

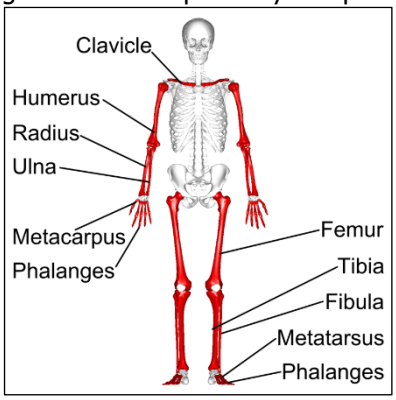
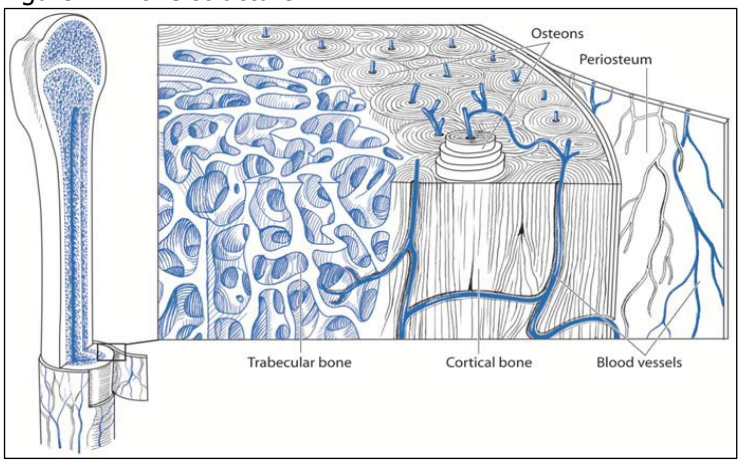


Figure 2: Bone structure[5]



Bone modeling

Throughout one's life, bone tissue undergoes a process of *modelling* and *remodeling* by which bone is made, adapted, maintained and repaired. The process of modelling is how bone is produced and occurs during the period of greatest bone formation from fetal development through adolescence[5]. In the modeling process, the size and shape of bones are changed in response to load bearing forces and physiologic factors. Bone remodeling is the process by which bone is repaired and maintained[25]. It is estimated that 5% to 10% of all the bone cells in an adult skeleton are remodeled each year[21,25]. Eighty percent of remodeling occurs within trabecular bone[21].

Modelling and remodeling processes involve three types of bone cells: osteoblasts, osteoclasts and osteocytes. Osteoblasts are responsible for creating bone tissue. Over a period of months, osteoblasts create an 'osteoid collagen matrix' which will form the new bone tissue. As osteoblasts form in layers and undergoes mineralization, new bone is formed creating new bone matrix. As new bone is formed some osteoblasts will remain on the bone surface as bone lining. Other osteoblast cells will differentiate into osteoclast cells forming the interior bone matrix. It is the osteoclasts which are responsible for dissolving bone cells[26].

Bone modeling and remodeling occurs in four distinct phases: Activation, Resorption, Reversal and Formation.[19]

Table 2: Bone Modeling Phases

Phase	Action	Duration
Activation	Activation is triggered by mechanical load force and chemical stimulation. This phase is characterized by the recruitment of osteoclast cell precursors. The osteoclast precursors bind to the bone surface. These pre-osteoclasts break down the endosteum/body lining cells.	
Resorption	The osteoclasts that have been recruited and have bounded to the bone during the previous 'Activation' phase begin to secrete protons via their ion channels. These protons lower the pH to 4.5 in the immediate area. The lower pH results in the bone lining being dissolved. Then additional chemicals are secreted thus further dissolving bone structure and forming 'saucer-shaped Howships' lacunae" on the bone surface[19]. The dissolved area forms the 'resorption pit'.	Two to four weeks
Reversal	Osteoblasts are recruited into the resorption pit. The osteoblasts create bone matrix.	Four to six months

Phase	Action	Duration
Formation	Osteoid are produced from osteoblast cells. Mineralization of osteoid cells marks the end of the formation phase.	

Peak Bone Mass

The amount of peak bone mass an that a 10% increase in the level of peak bone mass could reduce overall fracture risk by as much as 50%[27]. The studies have showed mixed effects of exercise on the peak bone mass attainment.[28] The maximum level of bone mass achieved by the end of skeletal maturation occurring by the late twenties[5]. Genetic and lifestyle factors influence the maximum level of peak bone mass achieved. Peak bone mass achievable is affected by genetic factors, which Is estimated to account for to 60%-80%[5,29,30] of the variation seen. Genetic factors that attribute to the obtainment of mass: 1) gender - males reach higher levels of peak bone mass than do females[31]; 2) race - Non-Hispanic blacks of both sexes reach higher levels of peak bone mass than either Caucasians or Asians[5,32]; 3) allele variants in vitamin D receptor[32] which affect osteocalcin levels. Environmental and lifestyle factors such as dietary consumption, exercise, smoking and alcohol consumption effect s peak bone mass but to a lesser extent (20-40%) then genetic factors. Lu *et al* found evidence that lean body mass (Lean body mass equals body weight minus body fat) may play a role in peak bone mass obtainment[33]. The effect of exercise in peak bone mass attainment appears to be most impactful when it occurs during one's developmental years.

Causes of Bone Loss

Bone mass is lost as one ages from all sites in the skeleton. Increases in the rate of remodeling of bone is observed with increasing age. More rapid loss during the years

immediately following menopause are seen primarily in the bones of the vertebra and neck[34]. During these first few years after the onset of menopause, the loss of bone mass ranges from one to five percent annually depending upon the individual. The menopausal related bone loss is driven by the decreasing levels of estrogen, as the low levels of estrogen leads to the death of osteoblasts[35].

Calcium is an essential element responsible for the vital functioning of the body's processes. As 90% of the body's calcium is stored within the bones, a deficiency of calcium within the body causes the calcium to be leached from the bones. This leaching of calcium can lead to a breakdown of the bone architecture and diminishment in bone strength. Vitamin D plays a role in building and maintaining strong bone architecture, through increasing the absorption of calcium.

Vitamin D in its essential state is inactive in the body and must undergo metabolism to render biologically active substance. Within the body, vitamin D is metabolized twice: first by the liver into 25-hydroxyvitamin D (25[OH]D) and then by the kidneys into 1,25-dihydroxyvitamin D (calcitriol)[36]. A deficiency of vitamin D can lead to a breakdown of bone structure.

Excessive alcohol intake[37] and smoking[38] have been found to be linked to a decrease in bone mass. Scientists have found an association between the use of certain medications and bone loss. Widely used in treatment of allergies and asthma, glucocorticoids (such as hydrocortisone or prednisone), can cause bone loss. Prolonged glucocorticoid use increases bone loss thorough multiple processes: decreasing absorption of calcium, decreasing production of sex steroids and growth hormones, decreasing calcium absorption, increasing death of osteoblasts and osteocytes while inhibiting the death of osteoclasts[35]. Certain chronic medical conditions such as rheumatoid arthritis, chronic kidney disease, chronic liver disease, Crohn's disease and some cancers (lymphoma, leukemia and myeloma) have been linked to the development of osteoporosis[21].

Bone Mineral Density and How to Measure It

Bone mineral density (BMD) is the standard measurement of the bone mineral content within bone. BMD is calculated by dividing the amount of bone mineral content in grams at a specific site in the body by the volume of bone at that specific site (g/cm^3)[35]. BMD indicates the amount of minerals within the bone and is an indicator of bone strength and fracture risk. The correlation between BMD and fracture risk has a strong inverse relation as BMD levels decrease, fracture risk increases[5].

The common technique used to measure BMD is dual-energy x-ray absorptiometry (DXA). DXA uses x-rays to measure bone mineral density value using area (g/cm^2). By measuring bone mineral content as an areal density and not volumetrically, DXA is more susceptible to mismeasurement due to bone size. This may lead to an overestimation of bone density in individuals with larger bones and an underestimation in those of smaller bones. The measurement of BMD score for osteoporosis diagnosis is commonly taken at the hip, femoral neck, lumbar spine and forearm.

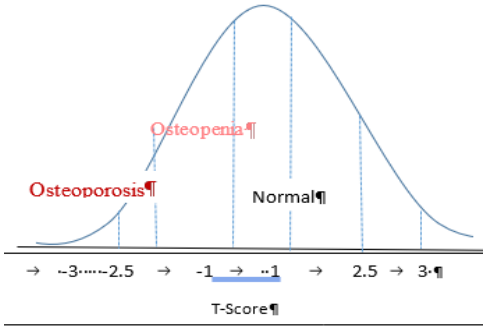
An individual's raw BMD value ($grams/cm^2$) alone does not provide meaningful and actionable information. To obtain standardized and clinically meaningful information, this raw value is compared to a normative value to calculate a T score or Z score. The referent group for calculating a T score is the expected mean values for young healthy adult of the same sex (e.g., comparing the BMD value obtained for a woman to the expected value for a normal young healthy adult female). The Z score referent score is for an expected mean value for a person of the same gender and age. The BMD value is then reported as the standard deviation from the referent score. For calculating the BMD T-scores the World Health Organization[1] and the International Society for Clinical Densitometry[39] recommend using the mean value for healthy, non-Hispanic white females aged 20-29 years for all females regardless of race. In the United States, the recommended reference values are drawn from the NHANES III 1988-1994 database[40].

Table 3: NHANES III 1988-1994 BMD Mean and Standard Deviation (SD) for Non-Hispanic white females aged 20-29 years by Anatomical Site[41]

Anatomical Site BMD (g/cm^2)	Mean	SD
Femoral neck	0.858	0.120
Trochanter	0.708	0.099
Intertrochanger	1.093	0.142
Total femur	0.942	0.122

The World Health Organization has set diagnostic categorization for osteoporosis and osteopenia[21]. A normal reading would be a BMD score <1 standard deviation (SD) below the mean normal referent score or a T score ≥ -1. Osteopenia is a condition where bone mass is lower than normal. A BMD between 1 and -2.5 SD below the mean referent score or a T score between -1 to -2.5 would represent osteopenia. Those diagnosed with osteopenia are seen as being at greater risk for the development of osteoporosis. Osteoporosis would be a reading >2.5 below the mean referent score or a T score ≤-2.5.

Figure 3: T score values for osteoporotic categories



Epidemiology of Osteoporosis and Osteoporotic Fracture

Worldwide prevalence of osteoporosis is estimated to be 200 million[5]. Within the United States, the National Osteoporosis Foundation estimated that over 43 million

Americans at least 50 years old had osteopenia or osteoporosis in 2002[5]. These numbers expected to increase to over 61 million by the year 2020[5].

Women suffer from osteoporosis disproportional compared to men. Prevalence estimates from nine countries (Australia, Canada, France, Germany, Italy, Japan, Spain, the United Kingdom and United States) found estimated osteoporosis prevalence ranging from 1 percent to 8 percent of men and 9% to 38% of women[42]. Using estimates from the National Health and Nutrition Examination Survey (NHANES) III, women were found to have a four-fold greater prevalence of osteoporosis when measured at the top hip or spine: 4% for men versus 16% for women[42].

Rates of osteopenia and osteoporosis are higher among non-Hispanic white women than among non-Hispanic black women. Bone mass density has been documented to range from 10% to 14% higher in postmenopausal non-Hispanic black women compared to non-Hispanic white postmenopausal women[43] . Overall, non-Hispanic black have been found to have lower rates of osteoporosis and osteopenia than all other racial/ethnic groups. It has been proposed that this difference is due to the higher levels of attainment of peak bone mass in non-Hispanic black compared to other races.

The most serious consequence of low bone mass is fracture. It is estimated that 9 million people worldwide have experienced a low bone mass related fracture[3], and within the United States, the estimate is 2 million[44]. Hip fractures alone are anticipated to rise to 6.3 million cases by the year 2050[21]. Hip fractures are the most serious form of osteoporotic fracture resulting in higher mortality, morbidity and healthcare resource costs than other types of fractures[45]. Lifetime risk for the occurrence of a hip fracture has been estimated to be 15% for white females[46].

Having suffered an initial fracture subsequently increases one's risk for having another fracture, regardless of the site of the initial fracture[47]. This risk is particularly higher during the first five years following the initial fracture[47]. Fractures increase one's risk of mortality and morbidity. It is estimated that 10% to 24% women who suffer a hip fracture

will die within one year of the fracture[10]. Results from the Women's Health Initiative study found that older age, a history of prior fracture and history of two or more falls was associated with subsequent fracture[10]. Regardless of race, there was an increase in fracture risk as the number of risk factors the individual has increases[10].

Hip fractures occur at a rate approximately 50% lower in non-Hispanic black women than in non-Hispanic white women. Despite those lower rates, non-white women in the United States experience fractures more commonly than they do chronic heart failure, stroke and breast cancer combined[10]. In spite of having a lower risk for suffering an osteoporotic fracture, non-Hispanic black who suffer an osteoporotic fracture experience poorer outcomes than do non-Hispanic whites: longer hospital stays, higher medical costs and higher readmission rates post fracture[44]. Outcomes for those with fracture worsen with increased age; this would explain these observations were seen in other studies showing that non-Hispanic black women were experiencing fractures at a greater age than non-Hispanic white females[47].

Risk factors for osteoporotic fractures have been well delineated for non-Hispanic white women but are not as well researched for non-Hispanic black women[45]. The following factors have been associated with fracture risk for non-Hispanic white women: Older age, race/ethnicity (being White or Asian), history of fracture after 54 years of age, smoking (current), history of treated diabetes and higher levels of fragility. In two studies[10], the only significant risk factors for osteoporosis and fracture risk was having a high school education or higher. Further examination on the link between educational attainment and fracture incidence needs to be done.

Chapter III

Methods

Research design

This study will be a retrospective database analysis to be conducted using the National Health and Nutrition Examination (NHANES) survey. The NHANES survey is conducted by the National Center for Health Statistics branch of the Centers for Disease Control and Prevention. The NHANES is cross-sectional survey that has annually surveyed a representative sample of the United States population since 1999.

Study Population

In this study, analyses will be conducted in all non-Hispanic black female and non-Hispanic white females aged 18 and older who participated in the NHANES surveys during 2007-2008 cycle and the 2009-2010 cycle.

Inclusion Criteria

- Age: 18 years and older
- Gender: Female
- Participated in an NHANES survey from 2007 to 2010
- Has DXA examination results in the NHANES database
- Non-Hispanic black participants in the NHANES surveys or
- Non-Hispanic white participants in the NHANES surveys

Exclusion Criteria

- Aged: 17 years and younger
- Male NHANES participants

- NHANES participants with missing race
- NHANES participants of multiple race
- NHANES participants of Hispanic ethnicity
- NHANES participants of Asian race
- Subjects missing DXA results in the NHANES database

Study Questions of Interest

1) What are the demographic and clinical characteristics of non-Hispanic black female survey participants with and without low bone mass and osteoporosis?
2) Among non-Hispanic black females, are there differences in the proportion of those with low bone mass (osteopenia) and osteoporosis across age groups?
3) As non-Hispanic black females on average have higher bone mass, would the use of a non-Hispanic black reference mean value (healthy, aged 20-29 years, non-Hispanic black females) be better than using of the standard healthy non-Hispanic white female aged 20-29 years of age?
4) Are there differences in clinical characteristics associated with low bone mass and osteoporosis among non-Hispanic black females aged 20-49 years compared with non-Hispanic black females aged 50 years and older?
5) Among non-Hispanic black female survey participants with BMD T-scores indicating osteopenia or osteoporosis,
    a. What is the proportion of participants who reported having been told they had osteoporosis or reported being treated for osteoporosis?
    b. Compared to non-Hispanic white female survey participants with BMD T-scores indicating osteopenia or osteoporosis, is there a difference in the proportion of those who reported having been told they had osteoporosis or reported being treated for osteoporosis?

Study Objectives:

1) To examine and compare the demographic and clinical characteristics associated with low bone mass (osteopenia) or osteoporosis for non-Hispanic black females and non-Hispanic white females.
2) To examine the prevalence of low bone mass (osteopenia) and osteoporosis by age, comparing non-Hispanic black females and non-Hispanic white females.
3) To examine the impact of using the reference mean value for healthy young (20-29-year-old) non-Hispanic black females in calculating the T score on the prevalence of low bone mass (osteopenia) and osteoporosis in non-Hispanic black female survey participants.
    a. To describe those who had discordant T-score classifications between the results using the non-Hispanic black referent and the standard referent.
    b. To identify characteristics associated with having a discordant result.
4) Examine the differences in characteristics associated with low bone mass (osteopenia) and osteoporosis between non-Hispanic black females 20-49 years compared to non-Hispanic black females aged 50 and older:
    a. T-score calculations using the standard reference mean value for healthy young (20-29-year-old) non-Hispanic white females.
    b. T-score calculations using the reference mean value for healthy young (20-29-year-old) non-Hispanic black females.
5) To compare the proportion of non-Hispanic black females to non-Hispanic white females with BMD T-scores indicating low bone mass (osteopenia) and osteoporosis who reported having been told they had osteoporosis or reported being treated for osteoporosis.

Key Variables of Interest

Demographics

- Age: The age of the participant at the time of the screening interview. Age will be classified as six levels:

  20 to 29

  30 to 39

  40 to 49

  50 to 59

  60 to 69

  70 and older

- Race: Will be defined as a combination of race and ethnicity grouped as

  Hispanic (including Mexican American) all races

  Non-Hispanic black

  Non-Hispanic white

  Other, including those of multi-races

- Height measured in centimeters
- Weight measured in kilograms
- Body Mass Index (BMI)

  Formula: $BMI = Weight / Height^2$

Table 4: Body Mass Index Classification

BMI	**Classification**
Below 18.5	Underweight
18.5 – 24.9	Normal or Healthy Weight
25.0 – 29.9	Overweight
30.0 and Above	Obese

- Education Level – the highest level of education level attained reported
- Household Income - the reported annual household income
- Smoking History – participants' smoking habits will be grouped as
    - Non-Smoker: those who reported never having smoked over 100 cigarettes in their lifetime and have not quit smoking or are using nicotine patches or similar products
    - Former Smoker: those who reported having smoked over 100 cigarettes in their lifetime but who are not currently smoking and indicated they had quit smoking
    - Current Smoker: those who reported having smoked over 100 cigarettes in their lifetime and reported to be currently smoking
- Alcohol Use – alcohol use will be classified as
    - Non-Drinker: Those who reported not drinking at least 12 alcohol drinks in a lifetime and has consumed zero alcohol drinks in the past 12 months.
    - Light to Moderate Drinker: Reported consuming on average 1 to 2 drinks per day over the past 12 months
    - Heavy Drinker: Reported consuming on average 3 or more drinks per day over the past 12 months or was a binge drinker (drinking 5 or more drinks in a day for at least 5 days per month). The World Health Organization used the consumption of 3 or more alcoholic drinks per day as a risk factor for osteoporosis[1].

Clinical Data

- Medications Used: Self-reported use

    Hypertensive medications, proton pump inhibitors (PPI), selective serotonine reuptake inhibitors (SSRI), Venlafaxine (SSNRI), antidiabetic medications,

bone resorption inhibitors, medications for cardiovascular disorders, estrogen, glucocorticoids, prednisone/cortisone and oral contraceptives.

- History of any fracture:
- History of low-impact fracture
    - Low-impact fractures will be defined as those resulting from a fall from standing height or less. All fractures either resulting from a hard fall or car accident will be excluded as will those who refused to answer or answered, "Don't know".
- Family history of hip fracture: Reported history that their mother or father broke their hip
- Family history of osteoporosis: Reported history that their mother or father had osteoporosis
- Duration of treatment with prednisone or cortisone
- Comorbid conditions (e.g. cancer, cardiovascular disease, chronic kidney disease, diabetes, rheumatoid arthritis, etc.)
- Menopausal status
- BMD measurements
- Calcium & Vitamin D levels and dietary intake
- Exercise activity level

Statistical Analysis Plan

For all statistical test, a p-value < 0.05 will be considered statistically significant. For categorical variables, will compare these by using chi-square or Fisher exact test as appropriate. All continuous variables (age) will be compared using t-test or nonparametric tests as appropriate. The appropriate survey sample weighting as recommended by the Centers for Disease Control and Prevention[48]. Missing data will not be imputed.

Analytic Datasets

There will be three analytic datasets that will be used as part of the analyses for this study:

1. **Initial Analytic Set**: This analytic set will consist of females surveyed as part of the 2007-2008 and 2009-2010 NHANES survey cycles who were interviewed and examined, were females aged 20 or older and were either classified as non-Hispanic white or non-Hispanic black.
2. **BMD Analytic Set**: This analytic set will be a subset of the initial analytic set consisting only of those who had valid BMD results.
3. **Main BMD**: This analytic set will be a subset of the BMD analytic set consisting only of non-Hispanic black females aged 20 old with valid BMD results.

Analysis plan by objective

For all statistical test, a p-value < 0.05 will be considered statistically significant. For categorical variables, will compare these by using chi-square or Fisher exact test as appropriate. All continuous variables (age) will be compared using t-test or nonparametric tests as appropriate. All statistical analyses will be conducted using SAS 9.4.

Objective 1: To examine the demographic and clinical characteristics associated with low bone mass or osteoporosis for non-Hispanic black females and non-Hispanic white females.

Analytic Dataset by to used: Initial Analytic Set

Clinical and demographic characteristics will be described by race (non-Hispanic black females and non-Hispanic white females). Calculate the proportion of non-Hispanic black female survey participants by bone mineral density status (normal, osteopenia and osteoporosis). Will conduct univariate analyses to examine the association of relationship between demographic and clinical characteristic and low bone mass or osteoporosis among non-Hispanic black females. Those clinical and demographic variables found to be significant in univariate analyses will be evaluated in logistic

regression analysis to determine what was independently associated low bone mass (osteopenia) and osteoporosis.

Objective 2: To examine the prevalence of low bone mass (osteopenia) and osteoporosis by age, comparing non-Hispanic black females and non-Hispanic white females.

Analytic Dataset by to used: BMD Analytic Set

Calculate the frequency of low bone mass (osteopenia) and osteoporosis by age group in non-Hispanic black females and non-Hispanic white females. Examine the correlations between age and total bone mineral density (gm/cm^2) and femoral neck bone mineral density (gm/cm^2).

Objective 3: To examine the impact of using the reference mean value for healthy young (20-29-year-old) non-Hispanic black females in calculating the T score on the proportion of low bone mass (osteopenia) and osteoporosis in non-Hispanic black female survey participants.

a. To describe those who had discordant T-score classifications between the results using the non-Hispanic black referent and the standard referent.
b. To identify characteristics associated with having a discordant result.

Analytic Dataset to be used: Main BMD Analytic Set

Compare the proportion of survey participants with either low bone mass (osteopenia) or osteoporosis based on the use of the standard reference mean value for young (20-29 year old) non-Hispanic white females versus the proportion of survey participants with either low bone mass (osteopenia) or osteoporosis based on the use of the reference mean value for young (20-29 year old) non-Hispanic black females. Describe the clinical and demographic characteristics associated with

discordant results. Those clinical and demographic variables found to be significant in univariate analyses will be evaluated in logistic regression analysis.

Objective 4: Examine the differences in characteristics associated with low bone mass (osteopenia) and osteoporosis between non-Hispanic black females 20-49 years compared to non-Hispanic black females aged 50 and older.

a. T-score calculations using the standard reference mean value for healthy young (20-29-year-old) non-Hispanic white females.
b. T-score calculations using the reference mean value for healthy young (20-29-year-old) non-Hispanic black females.

Analytic Dataset by to used: Main BMD Set

Comparing those clinical and demographic characteristics associated with low bone mass (osteopenia) and osteoporosis between non-Hispanic black females 20-49 years compared to non-Hispanic black females aged 50 and older. The comparison will be first completed for T-scores calculated using the standard reference mean values for healthy young (20-29-year-old) non-Hispanic white females and then for T-score calculations using the reference mean value for healthy young (20-29-year-old) non-Hispanic black females. Those variables found to be significant in univariate analyses will be evaluated in logistic regression analysis.

Objective 5: To compare the proportion of non-Hispanic black females to non-Hispanic white females with BMD T-scores indicating low bone mass (osteopenia) and osteoporosis who reported having been told they had osteoporosis or reported being treated for osteoporosis.

Analytic Dataset by to used: BMD Analytic Set

Compare the proportion of non-Hispanic black female survey participants with low bone mass (osteopenia) and osteoporosis who responded in the survey that they had been told they had osteoporosis or have been treated for osteoporosis to the proportion of non-Hispanic white females.

Chapter IV

Results

During the 2007-8 and 2009-10 NHANES survey cycles, a total of 20,015 survey participants were interviewed and had medical examinations [9,762 during the 2007-8 cycle and 10,253 during the 2009-10 cycle] (Table 5). Fifty percent (10,010) of the survey participants were female. Of the 10, 010 females surveyed, 6,040 (60.3%) were aged 20 years or older. Of the 4,044 non-Hispanic black surveyed, 1,173 (29.0%) were females aged 20 or older. A total of 3,972 female participants aged 20 and older were either non-Hispanic black females (n=1,173) or non-Hispanic white females (n-2,799) and comprised the initial analytic set. The primary focus of these analyses will be on the 1,173 non-Hispanic black females aged 20 or older. A limited comparison to a group of 2,799 non-Hispanic white females aged 20 or older will be conducted (Figure 4). Approximately 85% of those in the initial analytic set had BMD results and comprised the BMD analytic set (n=3,370).

Table 5: Unweighted Data from the 2007-2008 and 2009-2010 NHANES Survey Cycles

Characteristic	Number	Percentage
Gender		
Female	10,010	50.1
Male	10,005	49.9
	20, 015	
Race/Ethnicity		
Non-Hispanic Whites	8286	41.4

Characteristic	Number	Percentage
Non-Hispanic Black	4044	20.2
Mexican American	4369	21.8
Other	3316	16.6
Age Group		
0-19	8249	41.2
20-29	1889	9.4
30-39	1988	9.9
40-49	2014	10.1
50-59	1825	9.1
60-69	1910	9.5
70 and older	2140	10.7

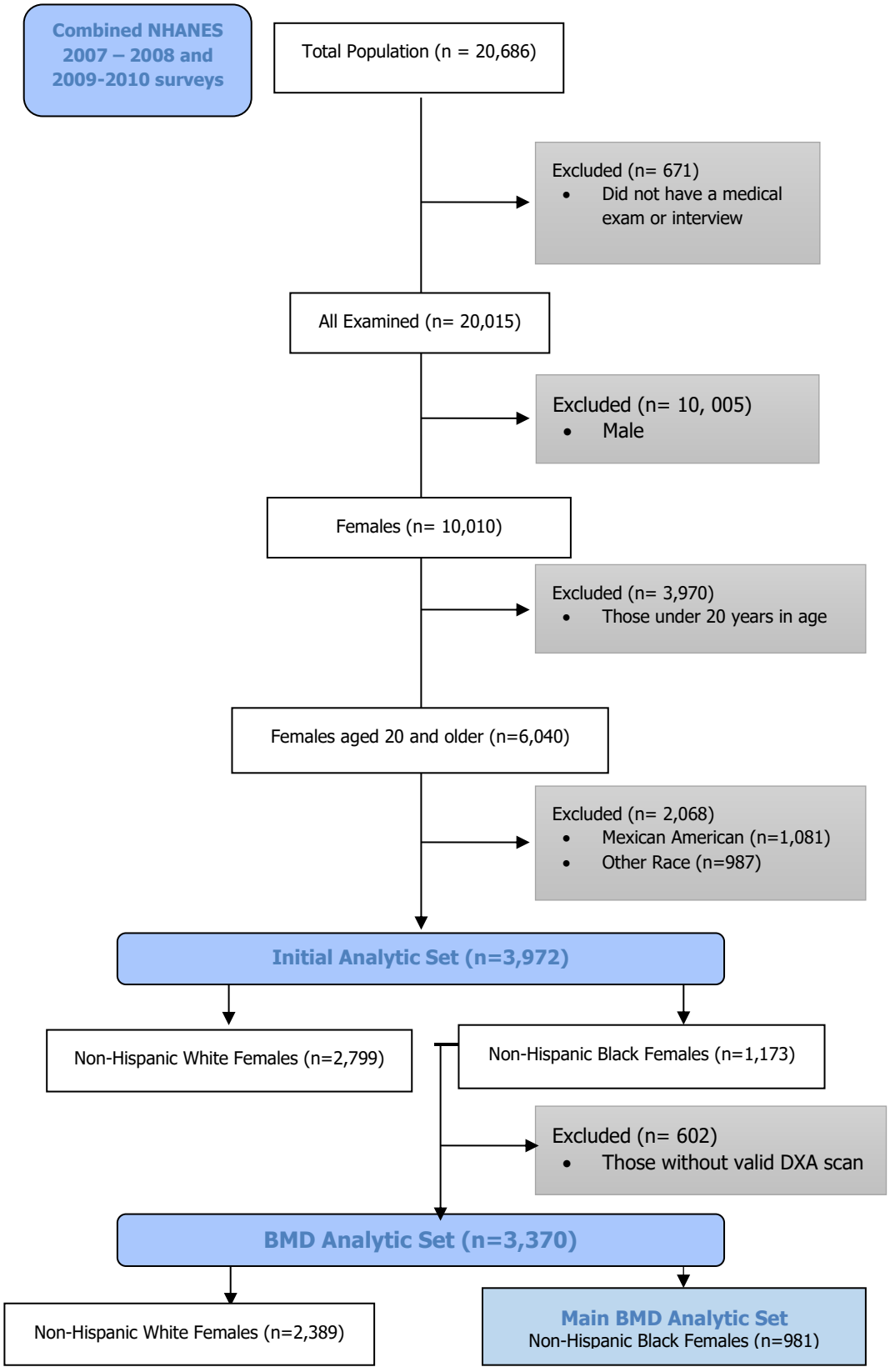
Table 6 presents demographic and clinical characteristics of the survey participants in the initial analytic population. Non-Hispanic black females were younger (45.0 years compared to 49.5 years) than Non-Hispanic white females ($p<0.0001$). There was a higher proportion of those aged 70 and older who were non-Hispanic white females (24.9%) compared to only 15.6% of non-Hispanic black females in this same age group. A higher percentage of non-Hispanic white had obtained a high school degree or beyond than did non-Hispanic black females (81.6% vs 71.1%, $p<0.0001$). A lower proportion of non-Hispanic black females reported being married than their non-Hispanic white female counterparts (29.4% vs 52.6%, $p<0.0001$). Having medical insurance was reported by 85.6% of non-Hispanic white and 79.6% of non-Hispanic black females ($p=0.001$): 49.7% of non-Hispanic white females reported being insured by private insurance compared to 48.1% of non-Hispanic black females). More non-Hispanic white females reported being either a

current or former smoker then non-Hispanic black females (44.2% vs 34.6% [p<0.0001]). Reported regular milk consumption was higher among non-Hispanic white females (74.5% vs 65.5% [p =0.0018]).

There were statistically significant differences in clinical characteristics between the two groups. Compared to Non-Hispanic black females, Non-Hispanic white females reported at higher rates of arthritis (37.0% vs 33.6%) and in particular osteoarthritis (41.4% [429/1036] vs 23.1% [91/394]), reported having been told they had cancer or a malignancy (15.1% vs 6.4%), having a thyroid problem (19.6% vs 10.3%) and being menopausal (39.4% vs 33.6%) (all significant at least p<0.05). Non-Hispanic white females reported at higher rates taking the following medications: bone resorption inhibitors, estrogen therapy, contraception, proton pump inhibitors, steroid use, or selective serotonine reuptake inhibitors or venlafaxine (all significant at least p<0.05). More non-Hispanic white females than their non-Hispanic black counterparts reported that their mother (15.7%) or their father (1.3%) had osteoporosis. Additionally, non-Hispanic white females reported at greater rates having a mother (7.2% vs. 2.7%) or father (2.5% vs 1.3%) who had experienced a fracture (p<0.05).

A higher percentage of non-Hispanic black females were obese (BMI of 30.0 or greater) than non-Hispanic white females (26.2% vs. 17.9%, <.0001). Compared to non-Hispanic white females, non-Hispanic black females reported significantly higher rates of having been told they had asthma or had experienced an asthma attack (29.5% vs 21.0%), had a close relative with diabetes (52.0% vs 35.7%), told they were diabetic or were taking insulin or pills for diabetes (18.2% vs 8.7%), reporting taking antidiabetic medications (16.0% vs 7.9%), were taking high blood pressure medications (26.1% vs 18.9%) and more reported having rheumatoid arthritis (29.9% vs 15.3%).

Figure 4: Final Study Population Flow Diagram



Fractures (Table 6)

A total of 489 non-Hispanic black and non-Hispanic white females reported having experienced a fracture of the hip, spine or wrist. Non-Hispanic white females experienced 84% (413/489) of the reported hip, spinal or wrist fractures ($p<0.0001$). Overall, spinal fractures were reported in 2.1% of the survey population of non-Hispanic white and non-Hispanic black females. More non-Hispanic white females reported having experienced a spinal fracture, 2.6% compared to 0.5% of non-Hispanic black females ($p<0.0001$). Wrist fractures were experienced by 11.2% of non-Hispanic white females compared to 5.4% of non-Hispanic black females ($p<0.0001$). There was no significant difference in the percentage of hip fractures experienced by non-Hispanic white females (1.6%) compared to 0.9% of non-Hispanic black females.

Osteoporosis (Table 6)

Eighty-five percent (3,370) of the 3,972 non-Hispanic white and non-Hispanic black females surveyed had a valid bone mineral density test result: 85.4% (2,389) of the non-Hispanic white females in the initial analytic set and 78.3% (918) of the non-Hispanic black females in the initial analytic set. Significantly more non-Hispanic white females had bone density results which qualified as either as osteopenia or osteoporotic [770 (32.2%)] compared to 190 (20.7%) of non-Hispanic blacks ($p<0.0001$). When you examine the trend of percentage of those classified as having a normal BMD T-score by age group, non-Hispanic black females have higher percentage of participants with normal BMD T-scores for all age groups then non-Hispanic white females (Figure 5). The percentage of those with normal BMD T-scores declined with increasing age for both non-Hispanic black and non-Hispanic white females (Figure 5). The decline in the percentage of normal BMD value for those aged 20 to 29 to the percentage for those 70 and older was slightly greater for non-Hispanic white females (-38.4% compared to -37.7%) (Figure 5). This trend held when examining the lowest mean BMD value by age group (Figure 6). When asked "Has a doctor

ever told you that you had osteoporosis, sometimes called thin or brittle bones?" or "Were you ever treated for osteoporosis?", a total of 431 (10.9%) reported having been told they had osteoporosis or reported being treated for osteoporosis.

Figure 5: Percentage of Participants with Normal BMD Scores by Race and Age

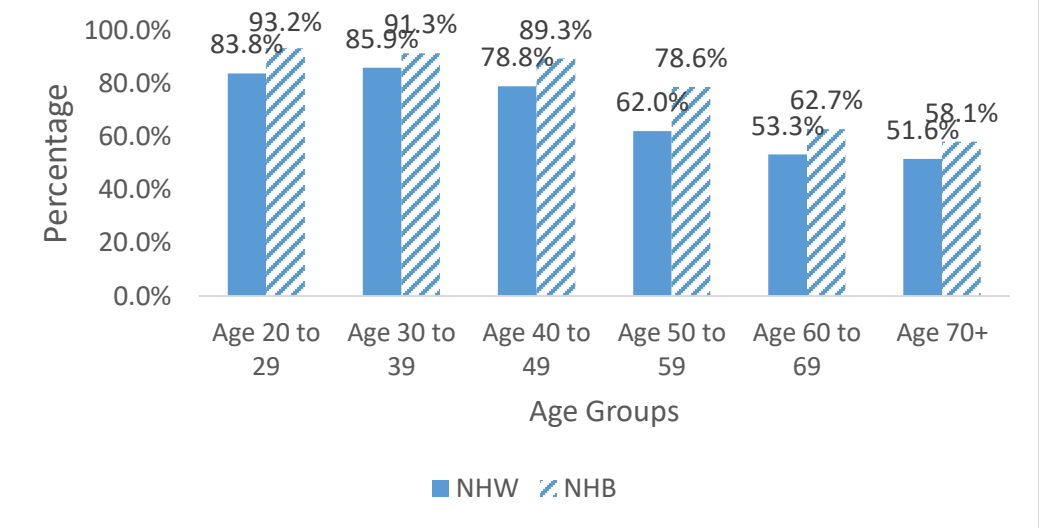
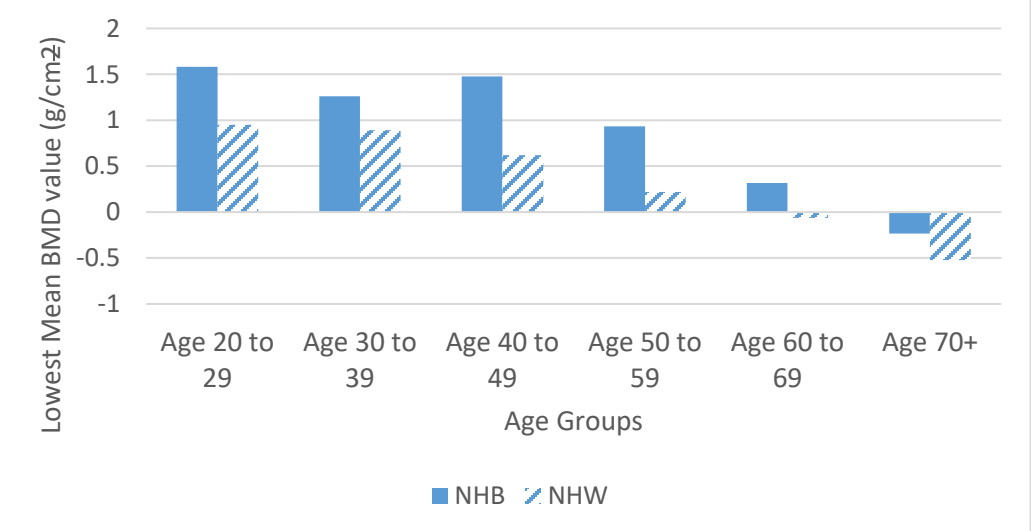


Figure 6: Lowest Mean T-Score by Age Group and Race



More non-Hispanic white females reported having been told they had osteoporosis or reported being treated for osteoporosis than did non-Hispanic black females: 364 (19.1%) vs. 67 (9.0%) [p<0.0001). Bone density test results were available for 80.7% (348) of the 431 who reported having been told they had osteoporosis or had received treatment. Of those with bone density test results, 47 were non-Hispanic black females and 301 were non-Hispanic white females. The concordance between self-reported osteoporosis or history or treatment and bone density test results indicating osteopenia or osteoporosis were lower among non-Hispanic black females. Nearly 43% (20/47) of non-Hispanic black females who reported they either were told they had osteoporosis or had been treated for osteoporosis were found to have normal bone density results when tested as part of the survey. This compared to 34% (103/301) of non-Hispanic white females who reported they either were told they had osteoporosis or were treated for osteoporosis were found to have had normal bone density results when tested. In both races, the proportion of those found on exam to have low bone mass (osteopenia) or osteoporosis and who reported having been either told they had osteoporosis or reported having received treatment was low. Of the two groups, a larger proportion of non-Hispanic white females with low bone mass or osteoporosis reported being told or having been treated compared to non-Hispanic black females : 29.7% (285/961) vs 21.9% (102/466) [p=0.002]. Parental history of osteoporosis or fracture was reported in 22.0% (617/2,799) of non-Hispanic white females and only 7.6% (89/1173) of non-Hispanic black females in the survey (p<0.0001).

As earlier noted, non-Hispanic black female participants sampled in the survey were younger on average than non-Hispanic white female participants. However, when you look at those with osteoporosis this was reversed (Table 7). Non-Hispanic black females with BMD values in the osteoporotic range had a higher mean age (69.5 years) than did non-Hispanic white females (62.7 years) in that range (Table 7). Among those with a BMD value classified as either normal or osteopenia, non-Hispanic white females had a higher mean age compared with non-Hispanic black females (46.4 years vs 43.2 years) (Table 7). The mean

age those with BMD values in the osteopenia range were 53.5 years for non-Hispanic black females and 56.0 years for non-Hispanic white females (Table 7).

The mean bone mass was marginally higher for non-Hispanic black females at the spinal site than non-Hispanic white females (Table 8). Similar results were observed for readings of the femur site. The mean calculated BMD T-scores at both anatomical site (femur and spinal) were higher for non-Hispanic black females when compared to non-Hispanic white females 1.10 vs 0.37 [Femur] and 0.14 vs -0.45 [Spinal] (Table 8). Age was found to be negatively correlated to both total femur BMD and spinal BMD for both non-Hispanic black and non-Hispanic white females (Table 8). For every year increase in age, total femur BMD decreased 0.43176 in non-Hispanic black females (<.0001) and decreased 0.45904 in non-Hispanic white females (<.0001) (Figures 7 and 8). The total spinal BMD declined 0.38178 for non-Hispanic black females (<.0001) and 0.37217 for non-Hispanic white females (<.0001) (Table 8, Figures 9 and 10).

Figure 7: Scatter Plot of Age by Total Femur BMD – Non-Hispanic Black Females

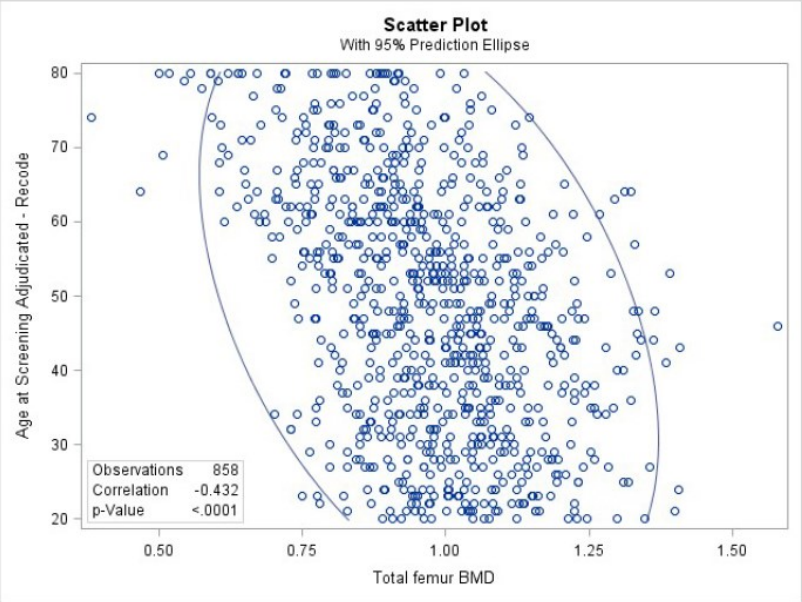


Figure 8: Scatter Plot of Age by Total Femur BMD – Non-Hispanic White Females

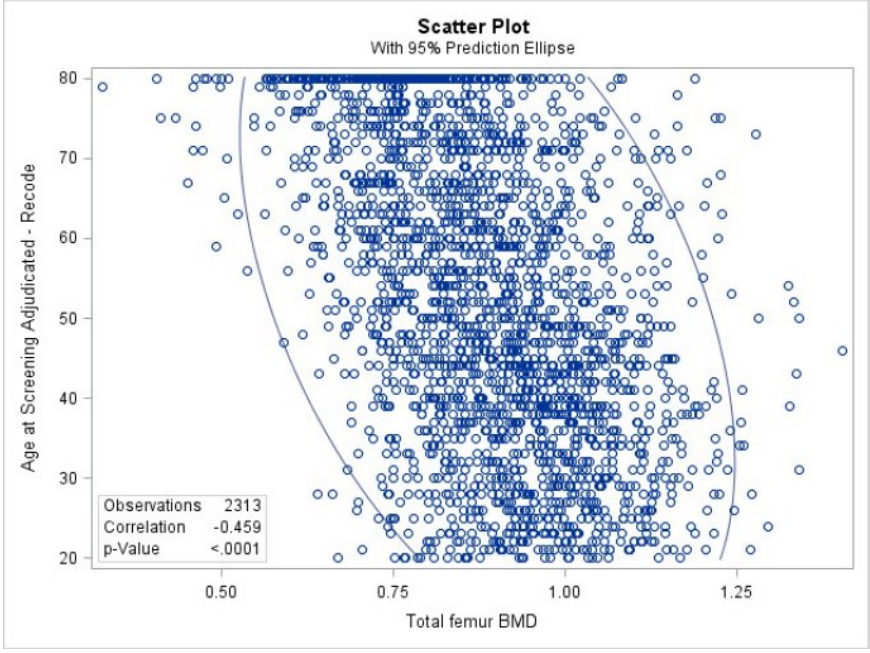


Figure 9: Scatter Plot of Age by Total Spinal BMD – Non-Hispanic Black Females

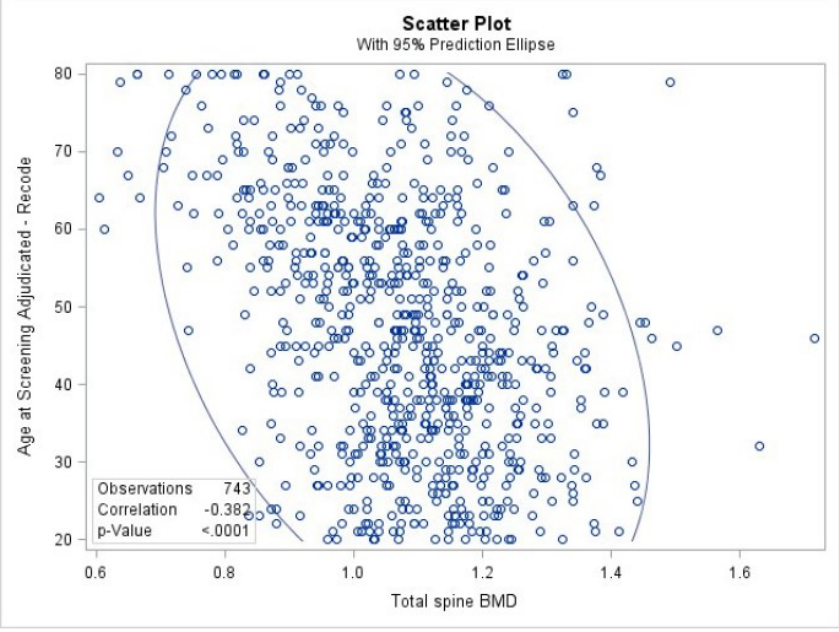
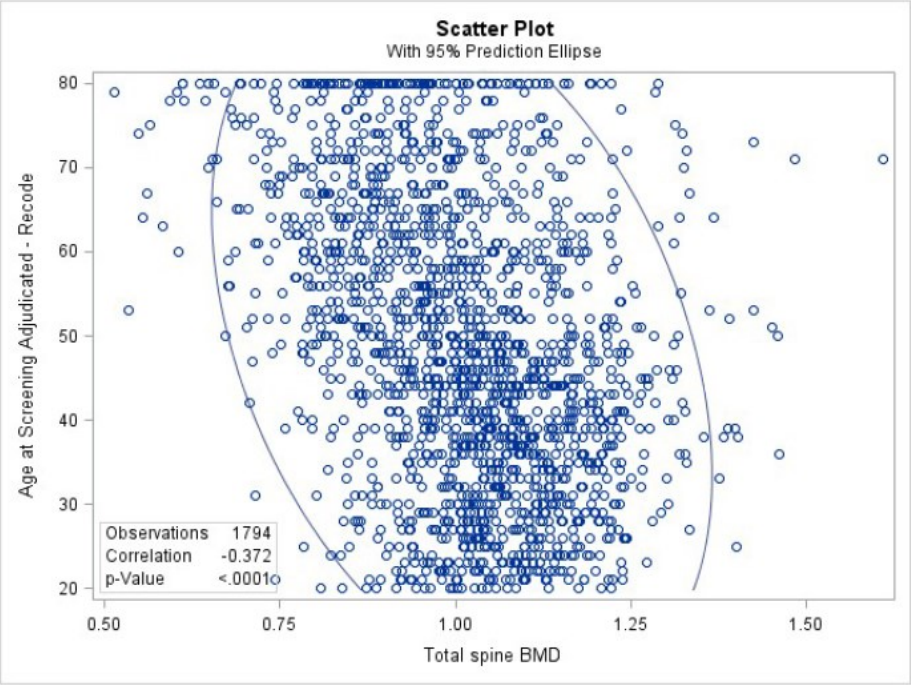


Figure 10: Scatter Plot of Age by Total Spine BMD – Non-Hispanic White Females



In looking at BMD status using the standard mean referent in only in non-Hispanic black female participants (Table 9), the following characteristics were found to be significantly associated with having osteopenia or osteoporosis: having less than a high school degree (odd ratio (OR) = 2.0, p<.0001), having arthritis (OR - 2.1, p<.0001), reported having high blood pressure (OR = 1.9, p<.0001), reported having heart disease (OR = 2.0, p=0.0199), being menopausal (OR = 4.2, p<0.0001), reported taking bone resorptive medication (OR = 15.5, p<0.0001), reported taking cardiovascular medications (OR = 2.2, p<.0001), reported taking diabetic medications (OR = 1.9, p=0.0015) and having reported having experienced a fracture at site other than the hip, spine or wrist (OR = 1.6, p=0.0223). Those who were found to be obese (BMI 30.0 or greater) were less likely to have low bone mass/osteopenia or osteoporosis (OR =0.4, =0.0086).

Compared to non-Hispanic black females aged 20 to 49, non-Hispanic black females aged 50 years and older were five times more likely to have BMD status of osteopenia or osteoporosis (p<.0001), they were also more likely to have other comorbidities: arthritis

(p<.0001), cancer (p<.0001), have diabetes or taking insulin (p<.0001), cardiovascular disease (p<.0001), high blood pressure (p<.0001), thyroid problems (p<.0001) or kidney disease (p=0.464). When analyses were limited to only those non-Hispanic black females aged 50 and older, this group were more likely to have osteopenia or osteoporosis if they had less than an a high school degree (OR = 1.8, p<.01), reported being menopausal (OR = 1.8, p=0.02) and reported taking bone resorptive medication (OR = 7.1, p<.001).

In logistic regression analysis of non-Hispanic black females, the following characteristics remained significantly associated with having osteopenia or osteoporosis: being 50 or older in age ($OR_{adjusted}$ =2.8, p = 0.0003), obtained less than a high school education ($OR_{adjusted}$ =1.6, p = .0236), being menopausal ($OR_{adjusted}$ =2.0, p = .0036) and being obese (BMI of 30.0 or greater) ($OR_{adjusted}$ 0.5, p = .003) (Table 10).

Recalculation of BMD T-score using non-Hispanic black mean referent

When BMD T-score values for non-Hispanic black females were calculated using the mean for healthy non-Hispanic black females aged 20-29 years instead of the standard formula which calculates the result using the mean of healthy, non-Hispanic white females aged 20-29 years, the BMD T-score at both anatomical sites decreased (Table 11). The calculated mean femur BMD T-score using the non-Hispanic black referent was 0.31 compared to 1.10 to the mean femur BMD T-score non-Hispanic white referent. The calculated mean spinal BMD T-score lowered to -0.30 when the non-Hispanic black referent was used compared to 0.17 when the standard referent is used (Table 11).

The percentage of non-Hispanic black females with a normal BMD T-score value classified as normal decreased by 11.5.% from 79.3% (using the mean standard referent) to 70.2% (using the mean value for young healthy non-Hispanic black females). Correspondingly, there was a 44% increase in those with either a BMD T-score classified as osteopenia or osteoporosis. The largest change observed was in those classified as having

osteopenia: 47.7% increase from 17.6% based on the standard referent to 26.0% when the non-Hispanic black female mean reference was used.

In comparing the BMD T-score results using the non-Hispanic black female reference to the values calculated by the standard referent, the majority (90.1%) of the results were concordant (Table 12). There were 91 (9.9%) participants whose results were found not be concordant. Of the 91, 84 (92.3%) had been classified as having a normal BMD T-score as per the standard referent calculation but had a BMD T-score value which now classified them as having osteopenia when the non-Hispanic black referent value was used. The remaining seven participants with discordant results moved from the osteopenia category to the osteoporosis category when the non-Hispanic black referent value was used (Table 12). The percentage of non-Hispanic black females aged 70 years or older with a normal BMD scores when calculated using the non-Hispanic black mean referent declined to only 43% compared to 58% when the non-Hispanic white mean referent was used (Figure 11).

Those non-Hispanic black females found to have low bone mass/osteopenia or osteoporosis when the non-Hispanic black referent was used in the calculation were more likely to be aged 50 or older ($OR_{adjusted}$ = 2.9, p<.0001), had obtained less than a high school education ($OR_{adjusted}$ =1.7, p = .0022), were menopausal ($OR_{adjusted}$ =1.8, p = .0093) and have a BMI of 30 or greater ($OR_{adjusted}$ = 0.5, p = .0008) (Table 13).

The 91 non-Hispanic black female participants with discordant classification of BMD T scores were on average significantly older than the 827 non-Hispanic black participants with concordant classification (52.3 years vs. 44.6 years, p<0.0001) (Table 14). A significantly higher percentage of those with discordant classification of BMD T-scores were menopausal (48.4% vs 34.6%), had experienced a hip fracture (2.2% vs 0.8%), were taking antidiabetic medications (28.6% vs 14.0%) and taking cardiovascular medications (44.0% vs 29.7%) (Table 14). Fewer participants with discordant BMD T-scores classification reported they had a close relative with asthma (20.9% vs 30.7%) or had a BMI of 30.0 or greater (16.5% vs

25.2%) (Table 14). Being 50 or older in age remained the only characteristics statistically significant with change in BMD classification ($OR_{adjusted}$ =2.2, p=.302) (Table 15).

Figure 11: Percentage of Non-Hispanic Black Females with Normal BMD Scores

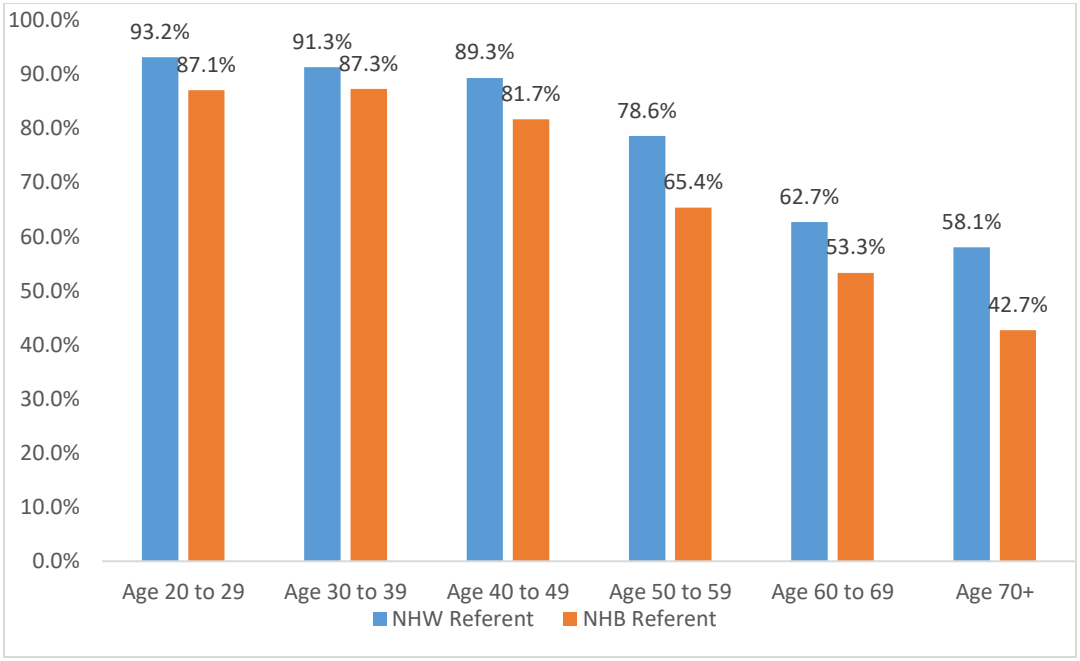


Table 6: Characteristics of Study Population of Interest: Non-Hispanic Black and Non-Hispanic White Females aged 20 or older

Characteristic	Non-Hispanic Black Females (%) Unweighted N = 1173	Weighted	Non-Hispanic White Females (%) Unweighted N = 2799	Weighted	P value
Mean Age	45.0		49.5		<0.0001
Age Group					<0.0001
20-29	204 (17.4)	5780323 (21.2)	381 (13.6)	24920389 (16.1)	
30-39	194 (16.5)	5445760 (19.9)	448 (16.0)	24401038 (15.8)	
40-49	202 (17.2)	5870667 (21.5)	487 (17.4)	29858393 (15.8)	
50-59	185 (15.8)	4652063 (17.0)	388 (13.9)	29059186 (19.3)	
60-69	205 (17.5)	28969703 (10.5)	398 (14.2)	21604526 (18.8)	
70 and older	183 (15.6)	2681610 (9.8)	697 (24.9)	24520438 (14.0)	
Education					<0.0001
High School or less	338 (28.8)	7083079 (25.9)	513 (18.3)	21876600 (14.1)	
High School Graduate or equivalent	278 (23.7)	635985 (23.9)	741 (26.5)	37847927 (24.5)	

Characteristic	Non-Hispanic Black Females (%)		Non-Hispanic White Females (%)		P value
	Unweighted N = 1173	Weighted	Unweighted N = 2799	Weighted	
Some College/AA	556 (42.7)	13660197 (50.0)	1542 (55.1)	94545999 (61.9)	
Marital Status					<0.0001
Married	345 (29.4)	8060611 (29.5)	1472 (52.6)	89092576 (57.7)	
Widowed	161 (13.7)	2470403 (9.0)	407 (14.5)	15667542 (10.1)	
Divorced	199 (17.0)	4416687 (16.2)	360 (12.9)	17780648 (11.5)	
Separated	54 (4.6)	1323950 (4.8)	56 (2.0)	2486886 (1.6)	
Never Married	334 (28.5)	8822225 (32.3)	355 (12.7)	20378034 (13.2)	
Living with partner	79 (6.7)	2179867 (8.0)	148 (5.3)	8832966 (5.7)	
Health Insurance					
Insured	934		2367		
Private	449 (48.1)	11308081 (53.8)	1177 (49.7)	8832966 (62.2)	0.0010
Public	485 (51.9)	9720259 (46.2)	1190 (50.3)	50557216 (37.8)	

Characteristic	Non-Hispanic Black Females (%) Unweighted N = 1173	Weighted	Non-Hispanic White Females (%) Unweighted N = 2799	Weighted	P value
Consumes 3 or more alcohol drinks per day	215 (18.3)	5375788 (3.0)	536 (20.1)	30978576 (17.1)	Not significant
Smoking Status					<0.0001
Never smoked	716 (61.0)	17108591 (9.7)	1486 (53.1)	86449924 (49.0)	
Ex-smoker	204 (17.4)	3963227(2.2)	678 (24.2)	37110488 (21.0)	
Currently smoked	210 (17.9)	5113053 (2.9)	559 (20.0)	26833364 (15.2)	
Reported Milk Consumption					0.0018
None	343 (29.0)	7923699 (4.4)	643 (23.0)	35827294 (19.7)	
Somewhat	62 (5.3)	1518867 (0.8)	70 (2.4)	3694767 (2.5)	
Regular	768 (65.5)	17857560 (9.8)	2086 (74.5)	114841909 (63.2)	
Clinical Characteristics					
Obese (BMI 30.0 or greater	307 (26.2)	7766860 (9.0)	501 (17.9)	24575415 (28.5)	<.0001

Characteristic	Non-Hispanic Black Females (%)		Non-Hispanic White Females (%)		P value
	Unweighted N = 1173	Weighted	Unweighted N = 2799	Weighted	
Doctor ever said they had arthritis	394 (33.6)	7578295 (27.8)	1036 (37.0)	48855800 (31.7)	0.03
Ever told they had asthma or had an attack in the past year	346 (29.5)	8400016 (31.2)	587 (21.0)	33035478 (21.8)	<0.0001
Ever told you had cancer or malignancy	75 (6.4)	1432880 (5.3)	423 (15.1)	19865284 (12.9)	<0.0001
Told they had diabetes or taking antidiabetic medication or at risk for diabetes	394 (33.6)	8414084 (30.9)	672 (24.0)	33898737 (22.1)	<0.0001
Ever told they had high blood pressure	569 (48.5)	11549072 (42.3)	998 (35.7)	47939886 (31.1)	<0.0001

Characteristic	Non-Hispanic Black Females (%)		Non-Hispanic White Females (%)		P value
	Unweighted N = 1173	Weighted	Unweighted N = 2799	Weighted	
Reported being told they had heart disease[1]	85 (7.2)	1470187 (5.4)	207 (7.4)	8059630 (5.2)	0.8417
Ever told they had a thyroid problem	121 (10.3)	2470539 (9.1)	548 (19.6)	28144492 (18.3)	<0.0001
Menopausal	394 (33.6)	7144686 (30.9)	1104 (39.4)	54310494 (39.3)	<0.0001
Reported taking the following medications:					
Bone resorption inhibitors	23 (2.0)	380776 (1.4)	145 (5.2)	6637401 (4.3)	<0.0001
Cardiovascular	385 (32.8)	7206902 (26.4)	778 (27.8)	35657488 (23.1)	0.085
Antidiabetic meds/insulin	188 (16.0)	3460759 (12.7)	220 (7.9)	10139724 (6.6)	<0.0001
Estrogen	17 (1.4)	329286 (1.2)	110 (3.9)	5631984 (3.6)	<0.0001
Glucosteroids	30 (2.6)	637867 (2.3)	48 (1.7)	2325963 (1.5)	0.0671

[1] Congestive heart failure, coronary heart disease, had angina/angina pectoris or had experienced an heart attack

Characteristic	Non-Hispanic Black Females (%)		Non-Hispanic White Females (%)		P value
	Unweighted N = 1173	Weighted	Unweighted N = 2799	Weighted	
High blood pressure	306 (26.1)	5916880 (3.3)	530 (18.9)	24187734 (15.7)	<0.0001
Oral contraceptives	32 (2.7)	899204 (0.5)	199 (7.1)	14165181 (7.8)	<0.0001
Proton pump inhibitors	113 (9.6)	2131748 (1.1)	370 (13.2)	18476839 (10.2)	0.0028
Selective serotonine reuptake inhibitors or venlafaxine	62 (5.3)	1391078 (0.8)	454 (16.2)	24918786 (13.7)	<0.0001
Reported steroid use	62 (5.3)	1327603 (0.7)	203 (7.3)	10449351 (5.8)	0.0128
Fracture History					
Reported having experienced wrist, spine or hip fracture	76 (6.5)	1647776 (0.9)	413 (14.8)	20486795 (11.3)	<0.0001
Wrist fracture	63 (5.4)	1381528 (0.8)	314 (11.2)	15549537 (8.6)	<0.0001

Characteristic	Non-Hispanic Black Females (%) Unweighted N = 1173	Weighted	Non-Hispanic White Females (%) Unweighted N = 2799	Weighted	P value
Hip fracture	11 (0.9)	239797 (0.1)	46 (1.6)	2072831 (1.1)	0.1701
Spinal fracture	6 (0.5)	133721 (0.1)	79 (2.8)	3952467 (2.2)	<0.0001
Reported having experienced a fracture at another site	175 (14.9)	3839787 (2.1)	703 (25.1)	36113221 (19.9)	<0.0001
Reported having experienced a low-impact fracture of wrist, spine or hip*	12 (1.0)	152704 (2.6)	87 (3.1)	3506493 (60.5)	0.3253
Low-impact wrist fracture	9 (10.6)	118586 (2.7)	60 (18.5)	245975 (56.6)	0.4730
Low-impact hip fracture	3 (0.3)	35284 (2.7)	22 (0.8)	861808 (67.0)	0.0754
Low-impact spinal fracture	1 (1.2)	11862 (3.9)	11 (0.4)	412181 (69.1)	0.0747

Characteristic	Non-Hispanic Black Females (%)		Non-Hispanic White Females (%)		P value
	Unweighted N = 1173	Weighted	Unweighted N = 2799	Weighted	
Reported having experienced a low-impact fracture at another site	135 (11.5)	3049057 (7.6)	475 (17.0)	23721936 (59.4)	0.0006
Reported mother had had a fracture	32 (2.7)	653364 (0.4)	202 (7.2)	9275178 (5.2)	<0.0001
Reported father had had a fracture	15 (1.3)	362081 (0.2)	70 (2.5)	3566682 (2.1)	0.0082
Osteoporosis History					
Reported having osteoporosis or reported being treated for osteoporosis	67 (5.7)	1264632 (0.7)	364 (13.0)	16202955 (9.0)	<0.0001
Reported a parent had osteoporosis or	89 (7.6)	2088680 (1.2)	617 (23.0)	34043566 (20.0)	<0.0001

Characteristic	Non-Hispanic Black Females (%) Unweighted N = 1173	Weighted	Non-Hispanic White Females (%) Unweighted N = 2799	Weighted	P value
had had a fracture					
Reported mother had osteoporosis	47 (4.0)	1196250 (0.7)	439 (15.7)	25869447 (14.9)	<0.0001
Reported father had osteoporosis	6 (0.5)	162254 (0.1)	36 (1.4)	2008884 (1.4)	0.0037
Osteoporotic Status (N)	918 (78.3%)	21636538	2389 (85.4%)	133795362	<0.0001
Normal	728 (79.3)	17994377 (83.2)	1619 (67.8)	94436389 (70.6)	
Osteopenia	162 (17.6)	3216472 (14.9)	654 (27.4)	34102275 (25.5)	
Osteoporosis	28 (3.1)	425689 (2.0)	116 (4.9)	5256699 (3.9)	

* Multiple fractures at different sites possible

Table 7: Osteoporosis Status by Mean Age and Race

	Non-Hispanic Black Females	Non-Hispanic White Females	Both Groups Combined
Normal	43.2	46.4	45.9
Osteopenia	53.5	56.0	55.8

Osteoporosis	69.5	62.7	63.2

Significantly statistically at <0.001

Table 8: Mean BMD (gm/cm²) and Correlation by Anatomical Site and Race

	Non-Hispanic Black Females	Non-Hispanic White Females
Mean Total Femur BMD	0.989822	0.902613
SE of the Mean	0.005602	0.003176
95% CI for the Mean	0.98-1.00	0.896-0.909
n	858	2313
Pearson Correlation Coefficients	-0.43176	-0.45904
	<.0001	<.0001
Mean Total Spinal BMD	1.092031	1.020206
SE of the Mean	0.006053	0.003094
95% CI for the Mean	1.08-1.10	1.01-1.03
n	743	1794
Pearson Correlation Coefficients	-0.38178	-0.37217
	<.0001	<.0001

Table 9: Significant Characteristics Associated with Osteopenia and Osteoporosis*: Non-Hispanic Black Females

	Odd Ratio (Unadjusted)	95% Lower CI	95% Upper CI	P-value
Obtained less than High School education	2.0	1.5	2.9	<.0001
Arthritis	2.1	1.5	2.9	<.0001
Obese (BMI 30.0 or greater)	0.4	0.2	0.8	0.0086

	Odd Ratio (Unadjusted)	95% Lower CI	95% Upper CI	P-value
Reported having high blood pressure	1.9	1.4	2.7	<.0001
Reported having heart disease	2.0	1.1	3.5	0.0199
Menopausal	4.2	3.0	6.0	<.0001
Reported taking cardiovascular medications	2.2	1.6	3.0	<.0001
Reported taking diabetic medications	1.9	1.3	2.9	0.0015
Reported having experienced a fracture at another site	1.6	1.1	2.5	0.0223
Aged 50 or older	5.1	3.5	7.4	<.0001

*Use of NHW reference

Table 10: Characteristics Significantly Associated with Osteopenia and Osteoporosis in Logistic Regression: Non-Hispanic Black Females

	Odd Ratio (adjusted)	95% Lower CI	95% Upper CI	P-value
Aged 50 or older	2.8	1.6	4.9	.0003
Obtained less than high school education	1.6	1.1	2.3	.0236
Menopausal	2.0	1.3	3.2	.0036
Obese (BMI of 30.0 or greater)	0.5	0.3	0.8	0.003

Table 11: Calculated T-score by Anatomical Site and Race by Mean Referent Calculation

	Non-Hispanic Black Females	Non-Hispanic White Females
Mean Femur T score using NHW referent	1.098514	0.371772
SE	0.046686	0.026471
95% CI	1.00-1.19	0.32-0.43
N	858	2313
Mean Femur T score using NHA referent	0.306321	
SE	0.043095	
95% CI	0.22-0.39	
N	858	
Mean Spinal T score using NHW referent	0.174187	-0.450381
SE	0.052633	0.026905
95% CI	0.07-0.28	-0.40 - -0.51
N	743	1794
Mean Spinal T score using NHA referent	-0.300479	
SE	0.042327	
95% CI	-0.21 - -0.39	
n	743	

Table 12: Comparison of BMD T-Score Classification Calculated using the Standard Referent Value and the BMD T-Score Classification Calculated using the Non-Hispanic Black Referent Value: Non-Hispanic Black Females Only

BMD T-Score Classification (Non-Hispanic White Referent Value)		BMD T-Score Classification (Non-Hispanic Black Referent)			
		Normal	Osteopenia	Osteoporosis	Total
	Normal	644	84	0	728
	Osteopenia	0	155	7	162

	Osteoporosis	0	0	28	28
	Total	644	239	35	918

Table 13: Characteristics Significantly Associated with Osteopenia and Osteoporosis in Logistic Regression: Non-Hispanic Black Females

BMD T-Score Classification based on Non-Hispanic Black Referent Calculation				
	Odd Ratio (adjusted)	95% Lower CI	95% Upper CI	P-value
Aged 50 or older	2.9	1.8	4.8	<.0001
Obtained less than High School education	1.7	1.7	2.5	.0022
Menopausal	1.8	1.1	2.7	.0093
Being obese (BMI of 30 or greater)	0.5	0.3	0.7	.0008

Table 14: Significant Differences in Clinical Characteristics Between Participants whose BMD T-Score Classification was Discordant Compared to Participants with Concordant BMD T-Score Classification When the Non-Hispanic Black Referent Value was Used: Non-Hispanic Black Females

	Discordant BMD T-Score Classification	Concordant BMD T-Score Classification	P-Value
N	91	827	
Mean Age in years	52.3	44.6	<0.0001
Age Group			
20-29	9 (9.9)	138 (16.7)	0.0036
30-39	6 (6.6)	144 (17.4)	
40-49	13 (14.3)	156 (18.9)	

	Discordant BMD T-Score Classification	Concordant BMD T-Score Classification	P-Value
50-59	21 (23.1)	138 (16.7)	
60-69	18 (19.8)	151 (8.3)	
70 and older	24 (26.4)	100 (12.1)	
Menopausal	44 (48.4%)	286 (34.6)	0.0006
Obese	15 (16.5%)	208 (25.2%)	0.009
Ever experienced a fracture of the hip	2 (2.2%)	7 (0.8%)	<0.0001
Taking an antidiabetic medication	26 (28.6)	116 (14.0)	0.0003
Taking a cardiovascular medication	40 (44.0)	246 (29.7)	0.0034
Had a close relative with asthma	19 (20.9%)	252 (30.7%)	0.0002

Table 15: Characteristics Significantly Associated with Osteopenia and Osteoporosis in Logistic Regression: Non-Hispanic Black Females – Difference between Concordant and Discordant Status

	Odd Ratio (adjusted)	95% Lower CI	95% Upper CI	P-value
Change in BMD T-score Classification				
Aged 50 or older	2.2	1.1	4.5	.0302

Chapter V

Discussion

In this analysis, approximately 20% of non-Hispanic black females were found to have BMD T-score values which were classified as low bone mass (osteopenia) or osteoporosis. Observed in this study population, the percentage of low bone mass (osteopenia) and osteoporosis increased with increasing age. Non-Hispanic black females with low bone mass (osteopenia) or osteoporosis were on average over 7 years older than their non-Hispanic white female counterparts. Rates of low bone mass (osteopenia) and osteoporosis observed in the current study were lower than the rates seen in a study by Siris *et al* of undiagnosed of low bone mineral density, 32% of non-Hispanic black females were found to have osteopenia and 4% had osteoporosis; although, the proportions of non-Hispanic black females with osteopenia or osteoporosis observed in their study were the lowest of any of the racial/ethnic groups, these numbers still represent a considerable risk for future fracture for non-Hispanic black females[49].

Both non-Hispanic black females and non-Hispanic white females have been documented to experience similar patterns of bone loss[50] and the same is true for men. In the current study, both non-Hispanic black and non-Hispanic white females were found to have increasing rates of low bone mass (osteopenia) and osteoporosis with increasing age. Age was strongly associated with the prevalence of low bone mass (osteopenia) or osteoporosis[51]. Bone mass declines with age; and given as non-Hispanic black females have on average higher bone mass, the impact of low bone mass (osteopenia) or osteoporosis will be seen as they reach a greater age than their non-Hispanic white counterparts.

Although the rate of self-reported hip fracture observed in this analysis among both non-Hispanic black and non-Hispanic white females were negligible, hip fracture is a major

contributor to osteoporotic-related morbidity and mortality. Mudano et al, found that both non-Hispanic black females and non-Hispanic white females reported similar rates of hip fracture[52]. As was observed in the current study, non-Hispanic black females in the Mudano study were older than non-Hispanic white females[52] which may have accounted for the equal percentages of hip fractures. It is this later age of onset for osteopenia and osteoporosis in non-Hispanic black females which may in part help to explain in their poorer outcomes that have been observed following a hip fracture[11,12,53] compared to non-Hispanic white females. In a cross-national analysis of incident hip fracture, hip fractures increased with age in all racial group, however, the rate of increase for non-Hispanic black females starting at age 60, a good 10 years later than what is observed in non-Hispanic white females[54].

Screening rates for osteoporosis despite national and international guidelines for screening for osteoporosis are low. Miller *et al* found that physicians were less likely to consider osteoporosis in their non-Hispanic black female patients, making fewer recommendations for BMD screening or recommend vitamin D and calcium supplementation[6]. It is not therefore surprising that rates of self-reported knowledge of osteoporosis status or treatment for osteoporosis in the current study were significantly lower for non-Hispanic black females than non-Hispanic white females. Cram et al[55], found similar results indicating non-Hispanic black females were less likely to know their BMD status. They suggested these differences in knowledge of their BMD status may be attributable to the healthcare disparities experienced by non-Hispanic black females[55]. Other researchers have found lower rates of osteoporosis screening[56] and treatment[57] in all non-Hispanic black females compared to non-Hispanic white females, including non-Hispanic black females at the highest risk for future fracture, those who had a history of a fracture[52] or who had had an incident fracture[58].

As non-Hispanic black females have on average higher bone density than non-Hispanic white females, is it critical to use the appropriate referent value when calculating the BMD T-score value. The currently used normal referent mean from healthy, non-Hispanic white females aged 20 to 29 may not be the most relevant for non-Hispanic black females.

This idea was explored in a 2005 study of osteopenia and osteoporosis among non-Hispanic blacks with rheumatoid arthritis[59]. Mikuls *et al* observed an approximately 116% increase in the number of those identified has having osteopenia or osteoporosis when the non-Hispanic black referent value was used as opposed to the non-Hispanic white referent value[59]. The change in the number of non-Hispanic blacks identified with osteopenia or osteoporosis increased by 44% in the current analysis when the non-Hispanic black referent value was used. Eighty-four individuals classified as having normal BMD T-score values using the standard referent to be classified as having a BMD T-score classified as osteopenia when the non-Hispanic black referent value was used. An additional seven, moved from being classified as osteopenia to being classified as having osteoporosis. As seen in the current analysis, those who changed were older and therefore would be greater risk for fractures and worse morbidity and mortality in the future. The mean age for those who changed was 52.3 years which was slightly lower for the overall mean age for those osteopenia (53.5 years) as calculated using the standard non-Hispanic white reference. This may indicate an opportunity for earlier identification and possible intervention if the non-Hispanic black referent is used. Although these clinical characteristics did not remain significant after adjusting for other factors, those whose classification changed did have more comorbidities (diabetes, cardiovascular disease and possible asthma risk) than whose status remain the unchanged.

BMD is predictive of possible future occurrence of fracture; however, as a single measure it does not consider the multifaceted nature of bone loss and omits other important clinical risk factors (age, sex, BMI, fracture history, current cigarette smoking, high alcohol consumption, parental hip fracture, long term use of oral glucocorticoid steroid, rheumatoid arthritis and other secondary causes of osteoporosis) associated with low bone mass (osteopenia) and osteoporosis[60]. The World Health Organization and the University of Sheffield have designed an algorithm for fracture risk assessment (FRAX) which incorporates clinical factors known to be associated with osteoporosis into a probabilistic model of a 10-

year fracture risk[61]. There is evidence that FRAX using both BMD and clinical information is better in predicting future fracture risk than just BMD alone[62-64], including in those without osteoporosis[65]. Looker *et al* conducted the first US nationally representative estimates of FRAX-based 10-year probabilities for hip and major osteoporotic fractures in adults aged 40 and older using the 2013-2014 NHANES survey[66] . They found that non-Hispanic black men and women had the lowest probabilities for 10-year probability for both hip and major osteoporotic fracture than other races and ethnicities[66]. However, the use of FRAX may still not be adequately sensitivity in predicting the future fracture risk for non-Hispanic blacks[67]. The FRAX utilities BMD based on the standard mean referent which may contribute to its lower sensitivity in this population.

The screening of non-Hispanic black females for low bone mass and osteoporosis remains vitality important. As is the use of more sensitivity assessment tools to more precisely identify those in this population who could benefit from fracture prevention plans (e.g., treatment, lifestyle changes and supplements).

Limitations

As the NHANES is a cross-sectional survey where potential exposure and outcomes are assessed at the same time, the assignment of causality will be not possible. Missing data may potentially introduce bias into the study if the missing data occurs in a nonrandom fashion. Answers to self-reported items may be subject to recall bias.

Chapter VI

SUMMARY AND CONCLUSIONS

Despite overall levels of higher bone mass density and lower fracture rates, non-Hispanic black females experience bone mass levels qualifying as osteopenia or osteoporosis in later years of life. This later onset increases their risk for adverse outcomes following an osteoporotic fracture. The calculation of the BMD T-score using the referent mean value for young (20-29-year-olds), healthy non-Hispanic black females instead of the standard for non-Hispanic white females were more sensitivity in detecting additional individuals with low bone mass (osteopenia) or osteoporosis. The use of the standardized BMD and FRAX may be of limited utility in distinguishing those members of a low-risk population who may actually have a higher risk of development osteoporosis and fracture. The use of a non-Hispanic black specific measure may lead to earlier detection and intervention in this population. Further investigations into measures specifically designed for this low-risk population is warranted.

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