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ABSTRACT

Title of Document: BONE MINERAL DENSITY AND HIP FRACTURE BY BODY MASS INDEX

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Research on the intersection of obesity and bone-related outcome such as osteoporosis and fracture risk is of significant public health concern as older adults will represent 20% of the US population by 2030; the majority of whom will have either or both conditions. The mechanical loading of extra weight is assumed to prevent osteoporosis and risk of fracture. However, half of all hip fractures occur among overweight or obese older adults. Many cross-sectional studies, including Paper 1 of this dissertation, find a protective effect of obesity on osteoporosis. Paper 1, using linear regression models and data from the National Health and Nutrition Examination Survey (NHANES 2005-2008) for adults ages $\geq$ 50 (n=3,296) found every unit increase in body mass index (BMI) was associated with a 0.0082 g/cm^2 increase in bone mineral density (BMD). However, Paper 2 of this dissertation using longitudinal data shows that obese older adults lose more bone density over time. Using multivariable generalized estimating equations and 10 years of data from 2,570 older adults in the Health, Aging, and Body Composition Study found that obese older adults lost 0.002 g/cm^2 of femoral neck BMD per year more compared with normal weight older adults ($p<0.001$). Prior literature on

obesity and risk of fracture is mixed, although the majority of studies, as well as Paper 3, find obesity to be protective against hip fracture risk. Cox proportional hazard models and data from 2,790 U.S. older adults in NHANES III linked to Medicare claims data (1991-2007) revealed obese older adults had a 15% lower risk of hip fracture (HR=0.85, 95% CI: 0.76, 0.96) while overweight older adults had the same risk level (HR=0.94, 95% CI: 0.85, 1.04) compared to normal weight older adults. The main strength of this dissertation was the comprehensive examination of obesity and bone-related outcomes using large diverse samples of older adults and multiple statistical methods. Future research should consider other measures of body composition and bone strength. Understanding the complex relationship between body mass, bone mass, and risk of fracture is pertinent, particularly as the majority of older adults are either overweight or obese.

BONE MINERAL DENSITY AND HIP FRACTURE BY BODY MASS INDEX

By
Jennifer Tower Lloyd

Dissertation submitted to the Faculty of the Graduate School of the
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DEDICATION

I would lovingly like to dedicate my dissertation to my mother, Dorothy Tower Lloyd, and my husband, Brett Marshall Wolter, both of which have earned an honorary doctoral degree through me by providing endless emotional and financial support. Your unwavering confidence in me has propelled me to the finish, thank you!

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None of us are as smart as all of us and my work

wouldn't be this good without any of you!

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CHAPTER 1. INTRODUCTION

1.1 STATEMENT OF THE PROBLEM

It had long been assumed that the mechanical loading of extra weight prevented osteoporosis and risk of hip fracture(Felson, Zhang, Hannan, & Anderson, 1993; Ravn et al., 1999; Reid et al., 1992). However, the increased prevalence of overweight and obesity among older adults has not resulted in a reduction of osteoporosis (Looker, Flegal, & Melton, 2007). To date, studies examining the relationship between obesity and osteoporosis have found inconsistent results(Beck et al., 2009; Greco et al., 2010; Lin et al., 2010; Nunez et al., 2007; Zhao et al., 2007). The majority of studies operationalize obesity with body mass index (BMI) and have largely found obesity to be protective against osteoporosis(Albala et al., 1996; Asomaning, Bertone-Johnson, Nasca, Hooven, & Pekow, 2006; Beck et al., 2009; Siris et al., 2001) However, numerous studies using other measures of obesity such as fat mass have it to be detrimental to bone mass (Bredella et al., 2010; Hsu et al., 2006; Nunez et al., 2007; Zhao et al., 2007). Moreover, due to the large prevalence of overweight and obesity among older adults, the majority of hip fractures actually occur in heavier older adults(Nielson, Srikanth, & Orwoll, 2012).

The aim of this study was to explicitly examine the cross-sectional and longitudinal association of bone mineral density (BMD) and incident hip fractures among overweight and obese older adults. This study uses three different datasets to comprehensively examine the association between overweight/obesity and bone-related outcomes.

1.2 SPECIFIC AIMS

Aim 1: Examine bone mineral density as it varies body mass index among older adults.

H1: Body mass index will be positively associated with bone mineral density.

Aim 2: Determine the rate of change in bone mineral density over time in overweight and obese older adults compared to normal weight older adults.

H2: Bone mineral density will decline more over time in normal weight compared to overweight or obese older adults.

Aim 3: Examine the risk of hip fracture by body mass index categories among older adults.

H3: Risk of hip fracture will be higher in normal weight compared to overweight or obese older adults.

CHAPTER 2. LITERATURE REVIEW

Individuals aged 65 and older are expected to account for 20% of the US population by 2030(Knickman & Snell, 2002). Demands on the health care system related to the aging population are feared to create a six-fold increase in Medicare spending(Schneider & Guralnik, 1990). Two diseases, osteoporosis and obesity, plague older adults and are associated with increased health utilization and spending. This chapter reviews current literature on 1) osteoporosis and risk of fracture; 2) overweight and obesity; and 3) the intersection of these two diseases among older adults.

2.1 OSTEOPOROSIS AND FRACTURE

Osteoporosis and osteopenia, diseases of the skeletal system, indicate low levels of bone mass and poor bone quality (Kanis, 2002a). Among Americans ages 50 years and older, 10 million have osteoporosis(National Osteoporosis Foundation, 2002). Over 33 million have osteopenia, a precursor for osteoporosis, with an expected 61 million by 2020(National Osteoporosis Foundation, 2002).

2.1.1 BONE MINERAL DENSITY (BMD)

BMD, a measure of bone strength, is the average amount of bone mineral in a given area(Cummings & Melton, 2002). BMD indicates the severity of osteoporosis and the risk of fracture(N. D. Nguyen, Pongchaiyakul, Center, Eisman, & Nguyen, 2005). Low BMD is associated with bone fragility and susceptibility to fracture(Albrand, Munoz, Sornay-Rendu, DuBoeuf, & Delmas, 2003a; Lips, 1997a; Snelling, Crespo, Schaeffer, Smith, & Walbourn, 2001a). Osteoporosis is defined as a BMD T score of 2.5

standard deviations below that of a young normal adult for persons age 50 years and older(Cosman, 2009). Osteopenia, often a precursor to osteoporosis, is defined by a BMD T score between -1.5 and -2.5(National Osteoporosis Foundation, 2002).

The dual energy x-ray absorptiometry (DXA) is used to measure BMD throughout the body(Cummings, Bates, & Black, 2002). DXA scans measure BMD at the hip (femoral neck or total hip), spine, and whole body. BMD measured at the femoral neck, hip, and whole body is a strong predictor of hip fractures (Cummings et al., 2002; Johnell et al., 2005; Schott et al., 1998). The prevalence of osteoporosis or osteopenia varies by site examined and even within sites such as the hip vs the femoral neck(Faulkner, von Stetten, & Miller, 1999). Risk of fracture also varies by site, and the strongest predictor of hip fracture is BMD measured at the hip(Cummings et al., 2002).

2.1.2 OSTEOPOROTIC FRACTURES

Osteoporosis and osteopenia place an older adult at increased risk of fracture(Albrand, Munoz, Sornay-Rendu, DuBoeuf, & Delmas, 2003b; Snelling, Crespo, Schaeffer, Smith, & Walbourn, 2001b). More than half of women age 50 and older will have an osteoporotic fracture in their lifetime(Chrischilles, Butler, Davis, & Wallace, 1991b). In 2005, there were 2 million osteoporotic fractures with an expected 3 million by 2025(Braithwaite, Col, & Wong, 2003). Fractures often result in disability, institutionalization, and death(Fransen et al., 2002; Magaziner et al., 1997; Magaziner et al., 2006). New onset functional impairments lead to extended or permanent institutionalization, accounting for the majority of costs associated with hip

fractures(Braithwaite et al., 2003). Osteoporotic fractures cost $17 million in 2005 with an expected $25 million in associated costs by 2025(Burge et al., 2007).

Osteoporotic fractures include vertebral and non-vertebral fractures. Non-vertebral fractures present more frequently to medical settings than do vertebral fractures. Risk of non-vertebral fracture, particularly hip fracture, increases with age(Melton, Crowson, & O'Fallon, 1999). Hip fractures are the most devastating type of non-vertebral fracture(Masud, McClung, & Geusens, 2009). Among individuals who've fractured a hip, 4% die while in the hospital and 24% die within a year of the facture(Magaziner, Simonsick, Kashner, Hebel, & Kenzora, 1989; Magaziner et al., 1997; Magaziner et al., 2003).

2.1.3 PREVALENCE OF OSTEOPOROSIS AND HIP FRACTURE BY DEMOGRAPHICS

Women age 50 and older represent 80% of the 10 million persons with osteoporosis (age 50 and older)(National Osteoporosis Foundation, 2002). In postmenopausal women, bone mass decreases as a result of reductions in estrogen(Albrand, Munoz, Sornay-Rendu, DuBoeuf, & Delmas, 2003b; Lips, 1997a; Snelling, Crespo, Schaeffer, Smith, & Walbourn, 2001b). Women have a higher incidence of hip fracture compared to men. In 2006, the rate of hip fracture was 4.97 among women and 2.09 among men(Ettinger, Black, Dawson-Hughes, Pressman, & Melton, 2010). Additionally, over half of women age 50 years with undiagnosed osteoporosis or osteopenia will have an osteoporotic fracture during their lifetime (Chrischilles, Butler, Davis, & Wallace, 1991a).

The incidence of hip fracture increases with age. The annual incidence of hip fractures among women age 50-54 was 0.29 in 2006(Ettinger et al., 2010), compared to an annual incidence of 26.05 among women aged 85 and older(Ettinger et al., 2010). The incidence of hip fractures has increased among certain age groups. For example, the incidence of hip fractures increased among individuals age 85+ since the 1990s(Ettinger et al., 2010). However, the incidence of hip fractures decreased during this same time period among individuals ages 50-69(Ettinger et al., 2010).

There are racial differences in the risk of osteoporosis, bone loss, and hip fracture. White older adults have a higher risk of osteoporosis compared to black older adults(Griffin, Ray, Fought, & Melton, 1992; Kessenich, 2000b; Peacock, Buckwalter, Persohn, Hangartner, Econs, & Hui, 2009b; Taaffe, Cauley, Danielson, Nevitt, Lang, Bauer, & Harris, 2001a). Black men have a slower rate of bone loss over time compared to white men(Tracy, Meyer, Flores, Wilson, & Hochberg, 2005). African American and Hispanic older adults have a lower risk of hip fracture compared to white older adults(Wolinsky et al., 2009).

2.2 OVERWEIGHT AND OBESITY

Aging is associated with a redistribution of body composition(Elia, 2001). Fat mass accumulates, particularly intra-abdominal fat, and muscle mass is lost or replaced with fat leaving older adults with a greater overall proportion of fat(Horber, Gruber, Thomi, Jensen, & Jaeger, 1997; Seidell & Visscher, 2000; Zamboni et al., 1997). The proportion of visceral fat also increases with age, which is associated with chronic diseases such as diabetes and cardiovascular disease(Beaufrere & Morio, 2000). Obesity

is associated with many detrimental chronic conditions(Bales & Buhr, 2008; McTigue, Hess, & Ziouras, 2006b) as well as a higher risk for the development of impaired mobility and physical function(Alley & Chang, 2007). Treatment for chronic conditions and disability related to obesity is estimated to cost $147 billion per year(Finkelstein, Chen, Prabhu, Trogdon, & Corso, 2007).

Overweight and obesity are the storage of extra body fat due to an unequal consumption and expenditure of energy(Khaodhiar, McCowen, & Blackburn, 1999; Zhao et al., 2008). Overweight and obesity are often operationalized by BMI. The correlation between BMI and the percentage of body fat ranges is relatively high, ranging from 0.73 to 0.93 in older adults(McTigue, Hess, & Ziouras, 2006a). BMI is defined by weight (kg)/height(m)^2. Typical BMI cut-points include <18.5 for underweight, 18.50-24.99 for normal weight, 25.0-29.99 for overweight, and 30 or greater for obese (National Institutes of Health (NIH) National Heart, Lung, and Blood Institute's (NHLBI) North American Association for the Study of Obesity (NAASO), 2000). Measured height and weight provide more accurate estimates of BMI compared with self-reported measures that underestimate the prevalence of obesity and overweight by 9.5% and 5.7%, respectively (Yun, Zhu, Black, & Brownson, 2006).

2.2.1 INCREASING PREVALENCE OF OVERWEIGHT AND OBESITY

The prevalence of excess weight has dramatically increased over time(Looker et al., 2007). The overall combined prevalence of overweight and obesity increased 6 percentage points between 1988-1994 and 1999-2002 (Looker et al., 2007). Currently over 70% of older adults are overweight or obese and this figure is expected to increase

to over 86% by 2030(M. C. Wang & Dixon, 2006; Y. Wang & Beydoun, 2007; Y. Wang & Beydoun, 2007; Y. C. Wang, Colditz, & Kuntz, 2007). Furthermore, future cohorts of older adults are at a higher risk of becoming obese(S. S. Guo, Wu, Chumlea, & Roche, 2002) and may have spent more of their lives obese(Leveille, Wee, & Iezzoni, 2005). This may result in negative health outcomes for newer cohorts of older adults who have spent a greater proportion of their lives obese compared to older birth cohorts, particularly since obesity is positivity associated with functional impairment and comorbid conditions (Alley & Chang, 2007; Alley, Chang, & Doshi, 2008; Bales & Buhr, 2008).

2.2.2 PREVALENCE OF OVERWEIGHT AND OBESITY BY DEMOGRAPHICS

There are important demographic differences in the prevalence of overweight and obesity by race, gender, and age. Non-Hispanic blacks and Hispanics have a higher prevalence of overweight and obesity compared with non-Hispanic whites (Flegal, Carroll, Ogden, & Curtin, 2010; Y. C. Wang et al., 2007). There are also important gender differences in the prevalence of overweight and obesity with men having a higher prevalence of compared to women (Flegal et al., 2010). Within the older population, the prevalence of obesity is highest in the younger old (~50 years old) compared to the oldest old (>70 years old) (Bales & Buhr, 2008; Y. Wang & Beydoun, 2007).

2.3 INTERSECTION OF OBESITY, OSTEOPOROSIS, AND FRACTURE

BMI is a strong predictor of bone mass (Felson et al., 1993; Glauber, Vollmer, Nevitt, Ensrud, & Orwoll, 1995; Margolis, Ensrud, Schreiner, & Tabor, 2000): the

correlation between BMI and BMD of the femoral neck is 0.47 among individuals age 50 and older (Looker et al., 2007). Cross-sectional studies have found a positive, linear relationship among BMI and BMD(Felson et al., 1993; Looker et al., 2007; Taggart, Craig, & McCoy, 2004). Studies examining change in BMD over time have found underweight individuals to be at higher risk of bone loss compared to overweight or obese individuals (De Laet et al., 2005; Margolis et al., 2000; Siris et al., 2001). Lastly, higher levels of body mass have been shown to reduce an individual's risk of hip fracture(De Laet et al., 2005; Ribot, Tremollieres, & Pouilles, 1994).

There are a number of potential explanations for the protective effect of excess body mass on BMD and hip fracture. First, obese individuals expose more load to their weight-bearing bones, which increases bone mass (Felson et al., 1993; Glauber et al., 1995; Ribot et al., 1994; Rosen & Bouxsein, 2006). Second, adipose tissue can convert androstenedione to the metabolically active estrogen, providing obese postmenopausal women with higher levels of estrogen(Felson et al., 1993). Higher levels of estrogen protect against bone loss(Ribot et al., 1994). Third, higher levels of body fat reduce the rate of bone resorption and have beneficial effects on BMD (Rosen & Bouxsein, 2006). Fourth, heavier body mass in early adulthood could affect peak BMD formation and increase overall levels of BMD (Felson et al., 1993; Ribot et al., 1994). Fifth, excess fat may protect against a fall by providing padding and potentially prevent a fracture (Beck et al., 2009). Lastly, low physical activity among obese and overweight individuals may reduce the opportunity for trauma (Beck et al., 2009).

2.3.1 CROSS-SECTIONAL ASSOCIATION

Numerous cross-sectional studies show a positive association between BMI and BMD in older women(Glauber et al., 1995; May, Murphy, & Khaw, 1994; Reid et al., 1992; Ribot et al., 1994). For example, increasing BMI is associated with decreased odds of having osteoporosis in postmenopausal women in the US(Siris et al., 2001). Therefore, obesity is thought to be protective against osteoporosis.

2.3.2 BONE LOSS OVER TIME

Longitudinal studies have found obesity to be associated with a reduced rate of bone loss(Reid, Ames, Evans, Sharpe, & Gamble, 1994; Ribot et al., 1994). Baseline BMI and change in BMD over time were positively associated in a UK population of older adults(Taggart et al., 2004). In an Australian population of older adults, individuals with higher weight at baseline lost less BMD over time compared with lower weight individuals (T. V. Nguyen, Sambrook, & Eisman, 1998). In this same study, the highest weight group experienced no bone loss. However, differences between prevalence estimates of obesity in these countries compared to the US make it difficult to compare study findings as the US has a higher prevalence of obesity compared to other countries.

2.3.3 INCIDENT HIP FRACTURE

Many studies have found overweight and obesity to be protective against risk of hip fracture (Ribot et al., 1994). The adjusted hazard ratio associated with risk of hip fracture for overweight and obese older adults in a nationally representative US sample was 0.77 and 0.40, respectively, indicating lower risk of hip fracture in both weight

groups (Wolinsky et al., 2009). Incident hip fractures were significantly lower in the overweight and obese groups compared to normal weight postmenopausal women (Beck et al., 2009). A retrospective study of risk of hip fracture found odds ratios for hip fracture of 0.926 and 0.862 for overweight and obese individuals, respectively (Gnudi, Sitta, & Lisi, 2009). A meta-analysis of 12 prospective international studies also confirmed this finding (De Laet et al., 2005).

2.3.4 INCONSISTENT FINDINGS RELATED TO OBESITY, OSTEOPOROSIS, AND HIP FRACTURE

Although it has been assumed that the mechanical loading of extra weight prevents osteoporosis and risk of hip fracture(Felson et al., 1993) (Ravn et al., 1999; Reid et al., 1992; Reid et al., 1994), the relationship between body and bone mass turns out to be more complicated and literature on this relationship is inconsistent(Cao, 2011). Cross-sectional studies using BMI as an indicator of adiposity have found obesity to be protective against osteoporosis(Albala et al., 1996; Armstrong et al., 2010). However, BMI is an imperfect proxy for fat mass. Studies that have directly assessed fat mass such as visceral fat have found it to be detrimental for bone(Bredella et al., 2010; Zhao et al., 2007). Moreover, the relationship between body and bone mass outcomes may be changing as recent cohorts of older adults have spent more of their lives obese(Leveille et al., 2005). Early exposure to high levels of fat mass may have deleterious impacts on the development of peak bone mineral density(Felson et al., 1993; Ribot et al., 1994) which could drastically increase risk of osteoporosis and facture earlier in life.

Increased bone mineral density among obese older adults does not clearly translate to reduced fracture risk: literature on obesity and fracture is mixed with some studies showing obesity to be protective against fracture(Beck et al., 2009; De Laet et al., 2005), while others indicating obesity increases fracture risk(Nielson et al., 2010; Premaor, Pilbrow, Tonkin, Parker, & Compston, 2010). Furthermore, the rise in the prevalence of obesity has not resulted in declines in the prevalence of osteoporosis (Looker et al., 2007). In fact, due to the large prevalence of overweight and obesity among older adults, the majority of fractures actually occur in heavier older adults (Nielson et al., 2012). For example among women, 46% of hip fractures occur in overweight and obese older adults compared to the 4% that occur in underweight older adults(Nielson et al., 2012). Lastly, the association between BMI and hip fracture may be non-linear. The well-understood risk of low body mass and low BMD does not infer that high body mass equals no risk of low BMD (De Laet et al., 2005; Gnudi et al., 2009).

CHAPTER 3. METHODS

3.1 OVERVIEW OF STUDY DESIGNS

The purpose of this study was to determine the association between BMI as it relates to 1) BMD, 2) change in BMD, and 3) incident hip fracture in older adults. Additionally, this study aimed to investigate effect modification between BMI and demographic factors in predicting the three study outcomes. Both cross-sectional and longitudinal analyses, broken into three research papers, were utilized to provide a comprehensive examination of the association of BMI, BMD, and hip fracture.

3.1.1 PAPER 1

The first research paper examined the cross-sectional association of BMI and BMD using publically available data from the 2005-2006 and 2007-2008 National Health and Nutrition Examination Survey (NHANES). This analysis tested effect modification by demographic factors to explore the association between BMI and BMD differed by age, gender, or race.

3.1.2 PAPER 2

The second research paper examined the longitudinal association between BMI categories (normal, overweight, and obese) and the rate of change in BMD over time using data from the Health Aging and Body Composition Study (Health ABC). Effect modification by demographic factors was examined to see if the association between BMI and change in BMD varied by age, gender, or race.

3.1.3 PAPER 3

The third research paper used longitudinal methods to examine the association between BMI categories (normal, overweight, and obese) and incident hip fracture using publically available data from NHANES III linked to restricted claims data from the Center for Medicare and Medicaid Services (CMS). This analysis tested effect modification by demographic factors and low BMD to see if the association between BMI and BMD varied by age, gender, or race.

3.2 OVERVIEW OF STUDY DATASETS

3.2.1 NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES)

NHANES is conducted annually throughout the US and interviews around 5,000 (final interviewed sample approximately 10,000) adults and children about health and nutrition status through interviews and physical exams (National Center for Health Statistics, 2009). The survey collects demographic, socioeconomic, dietary, and health related information through questionnaires as well as medical, physiological, and laboratory tests during examination. This study oversamples older adults as well as African Americans and Hispanics to produce reliable statistics of the US population. In addition to being nationally representative, the study contains measured height and weight for calculating BMI and measured BMD via DXA.

3.2.2 NHANES 2005-2008

NHANES 2005-2008 data are the latest NHANES series data available containing BMD of the femoral neck measured by DXA. This dataset includes over 5,000 individuals 50 years of age and older with over 4,800 individuals in the normal to obese BMI range. NHANES 2005-2008 data were used for Paper 1 to conduct a current analysis of the relationship between BMI and BMD in a nationally representative sample of older adults.

3.2.3 NHANES III

NHANES III data were collected in two phases between 1988-1994 and include close to 6,000 participants 60 years of age or older and over 5,000 participants in the normal to obese BMI range (National Center for Health Statistics, 1994). NHANES III has a complex survey design utilizing stratified multistage probability sample selection. This dataset was chosen for Paper 3 because of the linked NHANES participants to claims data providing up to 16 years of follow-up. Thus it provided the ability to observe an event (hip fracture) that has a low incidence rate per year. It also enabled the study to establish a temporal relationship between the independent and dependent variables.

3.2.4 MEDICARE LINKED FILES

Data from the NHANES III cohort were linked to Medicare claims data from CMS. CMS claims from 1991-2007 were linked to National Center for Health Statistics' (NCHS) participants through Medicare's Enrollment Database (EDB) (National Center for Health Statistics, 2010a). NCHS participants were matched based on social security

number (SSN), health insurance claims (HIC) number, last name, first name, middle initial, data of birth, sex, father's surname (women only), state of birth, and zip code using the master enrollment file, which has information on all individuals ever entitled to Medicare (National Center for Health Statistics, 2010a). To be eligible for the match, survey participants needed to provide their SSN or HIC during the NHANES interview as well as their date of birth and name. The linkage rate for individuals 65 years of age and older in NHANES III was 94% (95.8% among those considered eligible), resulting in 6,876 survey participants in NHANES III with linked CMS claims (National Center for Health Statistics, 2010a). The final sample size for Paper 3 was limited to study participants who agreed to CMS claims linkage and for whom NCHS was able to match with the Medicare records.

Although the NHANES III data spans 1988-1994, only data from 1991-1994 was used because CMS claims data are only available for years 1991-2007. For that reason, use of data from the 1991-1994 NHANES III data allowed a participant in the baseline cohort to have the opportunity to have Medicare claims available in the following year (ex: A participant in the 1991 NHANES study provided baseline data in that year and the first year of follow-up data for this participant was obtained from the 1992 CMS claims). Additionally, the analysis in Paper 3 was restricted to individuals ages 65 and over so that they were eligible to have Medicare claims within the follow-up time period.

These data are restricted and therefore required submitting an application to NCHS to gain access to de-identified data as well as using the data onsite (Hyattsville, MD) at the NCHS Research Data Center (National Center for Health Statistics, 2010b). There are costs associated with access and use of the restricted data. Fees included a

charge for setting up analysis files ($750 per day) and onsite data use ($300 per day, two day minimum) (National Center for Health Statistics, 2010c). Dr. Dawn Alley generously provided $2,000 of funding toward this project from a previous project sponsored by the Robert Wood Johnson Foundation Health and Society Scholars program.

3.2.5 HEALTH AGING AND BODY COMPOSITION

The Health ABC study, which began in 1997 with a baseline sample of 3,075 individuals age 70-79 (based in Memphis and Pittsburgh), follows a cohort of healthy (disability-free and cancer-free for 3 years prior to baseline survey) older adults (National Institute on Aging, 2009). Over 10 years of longitudinal follow-up data were available for the baseline sample of Paper 2. The study sample consisted of an equal number of men and women, of which more than a third were African American.

Participants were screened and determined eligible during a phone interview in 1997. A home interview was conducted before the clinic visit where questionnaire data were obtained on self-reported demographic information, health status, weight history, physical function and activity, work and volunteer activities, appetite and eating behavior, smoking and alcohol use, sleep habits, bodily pain, chronic conditions, cancer history (prior to the past three years as they would be ineligible to participate in the study), osteoporosis and falls, medical conditions, health care, and social support. Clinic visits were then scheduled and included performance measures, fasting blood sample, bone density scan (DXA), measured height and weight, cognition tests, as well as an inventory of medications being taken by the participant. Participants visited the clinic yearly for similar testing and answered questions about items that may have changed

since the last visit. A home visit, telephone interview, or a proxy interview may have been conducted if the participant was not able to come into the clinic or was not able to be interviewed.

Data from Health ABC were ideal for examining the longitudinal relationship between BMI and change in BMD in Paper 2. To obtain access to Health ABC data, a proposal was submitted the Health ABC Publications Committee for approval. The Health ABC proposal was approved on November 10, 2010 at which time I was granted online access to the study data.

3.3 OVERVIEW OF STUDY SAMPLES

The focus of this study was on older adults and therefore all study analyses were restricted to individuals at least 50 years of age or older. Underweight individuals were not included in any of the final samples as the focus of this study was on differences between normal, overweight, and obese older adults. The following table displays the main inclusion and exclusion criteria by study paper.

Table 1. Inclusion and Exclusion Criteria, by Study Paper

	Inclusion	**Exclusion**
Paper 1 (Cross-sectional, NHANES 2005-2008)		
Age $\geq$ 50 years	X	
Not missing values on BMI and BMD	X	
Underweight participants (BMI < 18.5)		X
Paper 2 (Longitudinal, Health ABC)		
Not missing values on baseline BMI and BMD	X	
Underweight participants (BMI < 18.5)		X
Paper 3 (Longitudinal, NHANES III)		
Age $\geq$ 65 years	X	
Not missing values on baseline BMI	X	
Linked to CMS claims	X	
NHANES respondent before 1991		X
Underweight participants (BMI < 18.5)		X

For Paper 1, individuals must have been 50 years of age or older and had non-missing measures for height, weight, and BMD. Underweight individuals (BMI < 18.5) will be excluded from the sample. Inclusion criteria for Paper 2 required individuals to have non-missing responses for baseline measures of height, weight, and BMD. Underweight individuals (BMI < 18.5) were excluded from the sample. Inclusion criteria for Paper 3 required individuals to be 65 years of age or older, have non-missing responses for baseline height and weight, to have been a respondent in 1991-1994, and to have been successfully linked to CMS claims data. Underweight individuals (BMI < 18.5) were excluded from the sample.

3.4 STUDY MEASURES

The following table details the variables in each of the study papers, including the dependent, independent, and covariate variables.

Table 2. Study Measures by Paper

	Paper		
Dependent Variables	**1**	**2**	**3**
BMD (DXA femoral neck) [continuous]	X		
BMD (DXA total hip, whole body, femoral neck years 1-10) [repeated measures]		X	
Hip fracture (CMS claims) [time to event]			X
Independent Variable	**1**	**2**	**3**
BMI (measured height/weight)	X	X	X
Covariates	**1**	**2**	**3**
Age	X	X	X
Sex	X	X	X
Race	X	X	X
Income (self-report)	X	X	X
Education level (self-report)	X	X	X
Marital status (self-report)	X		X
Vitamin D: self-report (food and supplement)	X	X	
Calcium: self-report	X	X	X
Lean muscle mass (total, excludes BMC)		X	
Fat mass (total, excludes BMC)		X	

Table 2 Continued

Weight change from greatest weight	X		
Weight change from age 50		X	
Study site		X	
Baseline BMD (DXA femoral neck)		X	X
Prior hip fracture (self-report)			X
Fall Frequency			X
Activity of daily living limitations (self-report)	X		X
Performance measures		X	X
Health status (self-reported health)	X	X	X
Chronic conditions			
Cardiovascular disease	X	X	X
Diabetes	X	X	X
Stroke	X	X	X
Hypertension		X	X
Thyroid	X		X
Cancer	X		X
Depression (self-report)	X	X	
Cognitive status		X	X
Prescription medications (bone active/depleting)	X	X	X
Smoking (self-report)	X	X	X
Alcohol (self-report)	X	X	X

3.5 JUSTIFICATION OF VARIABLE SELECTION

3.5.1. INDEPENDENT VARIABLE

Paper 1, 2, and 3 used baseline BMI as the independent variable for each set of analyses. BMI was selected over measures such as weight alone to represent body mass as it adjusts for differences in height between men and women and is more indicative of fatness (Asomaning et al., 2006). BMI is an effective measure for capturing the weight-bearing aspect of a heavier load on the skeleton (Beck et al., 2009; Reid, Plank, & Evans, 1992), but is not ideal for characterizing fat mass or fat distribution (Ribot et al., 1994; Zhao et al., 2007). Another limitation of this measure is that BMI may overestimate body mass among aging individuals who have lost height (Ribot et al., 1994). However, BMI was used in this study as it is a commonly used in large observational studies as it is a

quick and easy measure of body composition. More importantly, BMI is often used as a clinical measure for assessing risk of fracture(J. Compston et al., 2009; De Laet et al., 2005; Kanis et al., 2005; Kanis & Reginster, 2008), particularly in the absence of BMD.

3.5.2 DEPENDENT VARIABLES

The three study papers examined the spectrum of bone-related outcomes, including BMD (cross-sectionally and over time) and risk of hip fracture. Paper 1 examined the cross-sectional association between BMI and BMD in a national sample of older adults. BMD of the proximal femur was the dependent variable in this analysis. BMD is a measure of bone strength and has been shown to be highly associated with fracture outcomes (Cummings et al., 2002; Johnell et al., 2005). Therefore, femoral neck BMD was used as the main study outcome to serve as a proxy for risk of fracture. The femoral neck is a weight-bearing bone site and is most likely to benefit from higher body mass in an overweight or obese older adult through the mechanical loading of the extra mass on the bone site(Felson et al., 1993; Glauber et al., 1995; Ribot et al., 1994; Rosen & Bouxsein, 2006). Paper 2 examined the longitudinal association between BMI and change in BMD in a diverse sample of older adults. Change in BMD of the total hip, femoral neck, and whole body over time were the dependent variables in this analysis. Bone loss at these multiple BMD sites serve as proxy measures for risk of fracture (Cummings et al., 2002; Johnell et al., 2005). Lastly, Paper 3 examined the longitudinal association between BMI and risk of hip fracture, the most clinically relevant type of fracture, in a national sample of older adults. Hip fracture events are the most devastating

osteoporosis-related fractures that often result in disability and/or death (Magaziner et al., 1989; Magaziner et al., 1997; Magaziner et al., 2003; Masud et al., 2009).

3.5.3 EFFECT MODIFICATION

Effect modification was examined in each paper to determine if there were differences by age, gender, or race. Previous research on the relationship between overweight/obesity and osteoporosis/bone loss/fracture has not examined the varying effects of age, gender, and race, even though research has shown significant differences in these factor by demographic characteristics. Risk of osteoporosis, bone loss, and fracture increases with age(Albrand, Munoz, Sornay-Rendu, DuBoeuf, & Delmas, 2003b; Lips, 1997a), is higher in women than in men(Looker, Orwoll, Johnston, Lindsay, Wahner, Dunn, Calvo, Harris, & Heyse, 1997a), and is higher in whites than in blacks(Kessenich, 2000a; Peacock, Buckwalter, Persohn, Hangartner, Econs, & Hui, 2009a). Age, gender, and race also play an important role in the prevalence of overweight and obesity (Flegal et al., 2010). Fat mass increases with age until about age 70, after which it remains stable or declines(Hughes, Frontera, Roubenoff, Evans, & Singh, 2002; Kyle et al., 2001). Women tend to have a higher percentage of fat mass compared to men, but men tend to store more visceral fat compared to women(Blaak, 2001). White older adults also tend to have higher levels of visceral fat compared to African American older adults(Katzmarzyk et al., 2010). Previous research on the relationship between body mass and bone-related outcomes has been primarily conducted in white women, potentially ignoring important demographic differences in fat and bone mass.

3.5.4 CONFOUNDERS OF OVERWEIGHT AND OBESITY

There are a number of confounding variables associated with overweight and obesity that are controlled for in each of the three papers. Socioeconomic factors such as income, educational level, and marital status are associated with overweight/obesity and were controlled for in these analyses (El-Maouche, Xu, Cofrancesco, Dobs, & Brown, 2010;Y. Wang & Beydoun, 2007). High levels of BMI (overweight and obesity) are associated with physical disability, as measured by functional impairments and activities of daily living (ADL) limitations (Alley & Chang, 2007). Lower physical activity levels are associated with heavier weight among older adults (Folsom et al., 2000). BMI is associated with intake of dietary supplements such as calcium and vitamin D where higher levels of BMI are associated with lower odds of using supplements (Radimer et al., 2004; Ledikwe et al., 2003). Although the majority of older adults maintain stable weight over time, around 30% experience significant changes (increases or decreases) as they age (Newman et al., 2001). Obesity is highly associated with chronic diseases including hypertension, diabetes, thyroid disease, and cardiovascular disease (Alley & Chang, 2007; Khaodhiar et al., 1999; Michalaki et al., 2006; Villareal et al., 2005). Obese individuals have an increased risk for some types of cancer, including breast, colon, gallbladder, pancreas, renal, bladder, uterine, cervical, and prostate (Khaodhiar et al., 1999). Obesity is associated with impairment in mental health and fair/poor general health perceptions (Mokdad et al., 2003; Villareal, Banks, Siener, Sinacore, & Klein, 2004 ; Lahti-Koski, Pietinen, Heliovaara, & Vartiainen, 2002). Lastly, BMI is associated with smoking and alcohol consumption (Lahti-Koski et al., 2002).

3.5.5 CONFOUNDERS OF OSTEOPOROSIS, BONE LOSS, AND HIP FRACTURE

A number of confounding factors associated with osteoporosis/bone mass (many of which are also associated with overweight/obesity) were controlled for in Paper 1. Socioeconomic factors such as income, educational level, and marital status are also associated with osteoporosis (El-Maouche et al., 2010) (Navarro et al., 2009) (Elliot, Gilchrist, & Wells, 1996). Many chronic diseases are associated with osteoporosis, including cardiovascular disease, hypertension, diabetes, and stroke (Leidig-Bruckner & Ziegler, 2001; Poole, Reeve, & Warburton, 2002; Tanko et al., 2005). Treatment for many types of cancer (such as breast, prostate, testicular, Hodgkin's and non-Hodgkin's lymphoma, acute lymphatic leukemia, thyroid, and brain tumors) and thyroid diseases can increase likelihood of having osteoporosis (Pfeilschifter & Diel, 2000; Tannirandorn & Epstein, 2000). Poor self-rated health and depression have been shown to be associated with osteoporosis (Asomaning et al., 2006; Siris et al., 2001) (Cizza, Ravn, Chrousos, & Gold, 2001). Daily use of calcium and vitamin D have been shown to increase BMD over time (Karkkainen et al., 2010)(Moschonis, Katsaroli, Lyritis, & Manios, 2010)(Reid et al., 1994)(Wu, Ames, Clearwater, Evans, Gamble, & Reid, 2002a) (Jackson et al., 2006). Functional impairment increases as the severity of bone loss increases (Tsauo, Chien, & Yang, 2002). Bone-active medications, such as bisphosphonates, and bone-depleting medication, such as steroids, were controlled for as they are associated with increased or decreased BMD levels, respectively (MacLean et al., 2008; Piper & Gruntmanis, 2009; Van Staa, Leufkens, Abenhaim, Zhang, & Cooper, 2000) (Siris et al., 2001). Additionally, smoking and alcohol use are associated with low BMD and were controlled for in the regression analysis (Alekel et al., 1999; Brennan, Wactawski-Wende, Crespo, & Dmochowski, 2004; Siris et al., 2001).

Many similar confounding factors associated with bone loss/changes in bone mass were controlled for in Paper 2. Socioeconomic status, such as education, is associated with bone loss (Y. Wang & Beydoun, 2007). Functional limitations and many chronic conditions (such as cardiovascular disease, hypertension, diabetes, and stroke) are associated with higher rates of bone loss (Burger et al., 1998)(McFarlane, Muniyappa, Shin, Bahtiyar, & Sowers, 2004)(Schwartz et al., 2005) (Poole et al., 2002). Physical activity has been shown to be an important factor in the regulation of bone mass over time (Etherington et al., 1996) (Rikkonen et al., 2010)(Wilsgaard et al., 2009)(T. V. Nguyen et al., 1998). Medications for thyroid disease can increase the risk of bone loss (Pfeilschifter & Diel, 2000; Tannirandorn & Epstein, 2000). Poor self-rated health and depression have been shown to be associated with bone loss (Tolea, Black, Carter-Pokras, & Kling, 2007)(Cizza et al., 2001). Individuals with dementia or cognitive decline are at a greater risk for falls and hip fracture and some studies have also indicated these individuals are at a higher risk of bone loss (Z. Guo, Wills, Viitanen, Fastbom, & Winblad, 1998; Kipen, Helme, Wark, & Flicker, 1995; Sato, Asoh, & Oizumi, 1998). Weight change over time has been shown to impact changes in BMD (Beck et al., 2001)(Taggart et al., 2004) (Blain et al., 2004) (Ensrud et al., 2005)(Holbrook & Barrett-Connor, 1993)(T. V. Nguyen et al., 1998). Lean muscle mass and fat mass are significantly related to change in BMD over time (Marin, Pedrosa, Moreira-Pfrimer, Matsudo, & Lazaretti-Castro, 2010) (Reid et al., 1994) (Wu, Ames, Clearwater, Evans, Gamble, & Reid, 2002a) (Taaffe, Cauley, Danielson, Nevitt, Lang, Bauer, & Harris, 2001b). Bone active or bone depleting medication use was also controlled for as they are associated with increases or decreases in BMD over time, respectively (Wu, Ames,

Clearwater, Evans, Gamble, & Reid, 2002a). Lastly, smoking and alcohol use are associated bone loss and therefore are controlled for in the regression analysis (Wilsgaard et al., 2009)(Wu, Ames, Clearwater, Evans, Gamble, & Reid, 2002a).

Many confounding factors associated with risk of hip fracture were controlled for in Paper 3. Socioeconomic status is negatively associated with risk of hip fracture (Farahmand, Persson, Michaelsson, Baron, Parker et al., 2000). A number of health related variables were also controlled in this analysis because of their associations with hip fracture events. Physical activity has been shown to be associated with lower risk of hip fracture among older adults (DiPietro, Welch, Davis, Drane, & Macera, 1993; Farahmand, Persson, Michaelsson, Baron, Alberts et al., 2000; Feskanich, Willett, & Colditz, 2002). Calcium and vitamin D supplements are associated with reduced risk of hip fracture (DiPietro et al., 1993)(Bischoff-Ferrari et al., 2005; Boonen et al., 2007). Factors predictive of falls such as slow gait speed and difficulty walking tandem have been shown to increase risk of hip fracture (D'Agostino RB et al., 2008). Fair or poor self-reported health status is associated with the occurrence of hip fracture events (Siris et al., 2001). Older adults with dementia and cognitive impairment are at a higher risk of falling (van Doorn et al., 2003)(Kanis, 2002b; Taylor et al., 2004). Chronic diseases such as hypertension, cardiovascular disease, stroke, and thyroid are associated with an increased risk of hip fracture (Mussolino, Looker, Madans, Langlois, & Orwoll, 1998). A prior hip fracture event places an individual at an increased risk for subsequent hip fracture occurrence (Kanis et al., 2004). Individuals experiencing a higher number of falls are also at a greater risk of hip fracture (Cumming & Klineberg, 1994). Cancer treatment is associated with bone loss and therefore an increased risk of hip fracture (Alibhai et al.,

2010; Neuner, Yen, Sparapani, Laud, & Nattinger, 2010). Uses of medications known to deplete bone (steroids) are associated with an increased risk of hip fracture (Van Staa et al., 2000). Similarly, medications associated with increasing bone mass, such as bisphosphonates, are associated with reduced risk of hip fracture (MacLean et al., 2008; Piper & Gruntmanis, 2009). Smoking increasing the risk of hip fracture as smoking is associated with bone loss (DiPietro et al., 1993; Law & Hackshaw, 1997; Wilsgaard et al., 2009). Alcohol intake has been shown to be detrimental to bone health and has been associated with an increased risk of hip fracture (Kanis, Johansson et al., 2005).

3.6 OPERATIONALIZATION OF VARIABLES

3.6.1 PAPER 1

Using recent data from NHANES 2005-2008, Aim 1 examined the association between BMI and BMD in a cross-sectional analysis. The dependent variable in Aim 1 was a continuous measure of BMD (femoral neck), which was measured through DXA scans of the femur, defined as g/cm^2. The main independent variable for Aim 1 was a continuous measure of BMI calculated from measured height and weight (weight in kilograms divided by height in meters squared). Age, sex, and race were examined as effect modifiers between the BMI and BMD association. Interactions terms were created between BMI (continuous) and age (continuous); race (1=white; 0=nonwhite); and sex (1=female; 0=male).

There were a number of covariates that were included in the regression model. These included a continuous variable of self-reported physical activity (Global Physical Activity Questionnaire(World Health Organization, 2010)) based on metabolic equivalent

(MET) scores(World Health Organization, 2010); a continuous measure of calcium, which comes from self-reported intake of food and supplements(Feskanich et al., 2002; Karkkainen et al., 2010); a continuous measure of vitamin D based on self-reported intake of food and supplements; a continuous variable indicating the sum of weight change since greatest weight and survey year weight; prior hip fracture (dichotomous variable based on self-report); family income (continuous); education (indicator variables for less than high school, high school graduate, greater than high school); marital status (indicator variables for married vs not married); depression status (continuous) assessed by the Depression Screener which contains questions from the Patient Health Questionnaire (a nine-question survey instrument based on DSM-IV signs and symptoms of depression in the past two weeks) (Kroenke, Spitzer, & Williams, 2001; Spitzer, 1999); chronic conditions assessed by self-report (dichotomous variables for the presence of high blood pressure, cardiovascular disease, diabetes, stroke, and thyroid disease); self-reported cancer (1=yes; 0=no); self-reported health status (indicator variables for excellent/ very good/good vs fair/poor); dichotomous variable for indication of self-reported use of medications that are bone-active (bisphosphonates) and bone-depleting (steroids); a count of activities of daily living (ADL) limitations (getting in and out of bed, eating, and dressing); current smoking status (dichotomous measure based on self-report) and average use of alcohol per day in past year (continuous).

3.6.2 PAPER 2

Using multiple years of data from Health ABC, Paper 2 examined the association between baseline BMI and the rate of change in BMD over time. The outcome measure

for Paper 2 was BMD from year 1 (1997-1998) to year 10 (2007-2008). BMD was obtained from DXA measurements of the total hip, femoral neck, and whole body and measured by g/cm^2. The main independent variables for Paper 2 included normal to obese BMI categories [BMI categories range from 18.5 to 24.9 for normal weight, 25 to 29.9 for overweight, and $\geq$ to 30 for obese]. The BMI categories were calculated by measured height and weight (weight in kilograms divided by height in meters squared). Age, gender, and race were examined as effect modifiers between baseline BMI and the rate of change in BMD over time. Interactions terms were created between BMI (overweight and obese) and age (continuous), race (1=white; 0=nonwhite), and sex (1=female; 0=male).

There were a number of covariates included in regression models that were measured at baseline. Although measurements of most of these variables are available at follow-up time points, time varying covariates are not be examined in this current study. This was determined as little is known about the association between baseline BMI and change in BMD across the full BMI spectrum and it is preferred to examine baseline associations before variables changing over time are examined. Covariates included family income (continuous); education (indicator variables for less than high school education, high school graduate, more than high school education); site (1=Memphis, 0=Pittsburgh); physical activity (continuous, based on a sum of self-reported exercise total kcal/kg/week and kcal/week from walking and exercise)(Ainsworth et al., 1993; Ainsworth et al., 2000); dichotomous measures of calcium and vitamin D (total of self-reported supplements); lean muscle mass (continuous, based on whole body DXA of total fat free mass, gm); fat mass (continuous, based on whole body DXA for total fat, gm); weight change from age 50 (continuous, based on self-report to the following survey

question “What was your usual weight at about age 50? ”), depression status (continuous, based on the Center for Epidemiologic Studies Depression Scale CES-D) (Radloff, 1977); score on Teng Mini-Mental State Exam to determine dementia status (continuous), chronic conditions based on a combination of self-report, medication use, and diagnosis (dichotomous variables for cardiovascular disease and hypertension); self-reported stroke and thyroid disease, self-reported health status (indicator variable for excellent/very good, good, fair/poor); dichotomous variable for self-reported use of medications that are bone-active (bisphosphonates) and bone-depleting (steroids); a count of activities of daily living (ADL) limitations (getting in and out of bed, eating, dressing); a continuous variable of physical performance measures based on the Short Physical Performance Battery (SPPB) which includes usual walk, narrow walk, chair stands, and standing balance; current smoking status (dichotomous measure based on self-report); and frequency of alcohol use (continuous variable based on self-report of drinking within the past year .

3.6.3 PAPER 3

Using longitudinal data from NHANES III linked to CMS claims, Paper 3 investigated the association between incident hip fracture and baseline BMI status. The dependent variable for Paper 3 was time to event (hip fracture). Hip fracture events were measured for up to 10 years after baseline and were obtained from CMS claims based on ICD-9 codes 820.*xx*. Observations were right censored if the participant was lost to follow-up or died during the follow-up period. The main independent variable for Aim 3, BMI categories, was measured at baseline and included normal, overweight, and obese

BMI status. Body mass status was obtained from BMI calculated by measured height and weight (weight in kilograms divided by height in meters squared). BMI categories ranged from 18.5 to 24.9 for normal weight, 25 to 29.9 for overweight, and $\geq$ to 30 for obese. Interaction terms between baseline BMI and age (1=age $\geq$73, 0=age<73), sex (1=female; 0=male), and race (1=white; 0=nonwhite).

There were a number of confounders measured at baseline that were included in regression models. These include family income (continuous); education (indicator variables for less than high school, high school graduate, greater than high school); low BMD (1=BMD $\leq$0.90 g/cm^2 in women and $\leq$0.82 g/cm^{2}on men, 0=normal BMD); physical activity (10 self- reports on walking, jogging, bike riding, swimming, aerobics, dancing, calisthenics, gardening, lifting weights, and other activities within the past month and the intensity level of each activity based on metabolic equivalent (MET) scores recommended cut points(Ainsworth et al., 1993); calcium (continuous, self-report of dietary supplements); vitamin D (continuous, self-report of dietary supplements); weight change since greatest weight (continuous); fall frequency within past year and prior hip fracture (dichotomous variables based on self-report); chronic conditions assessed by self-report (dichotomous variables for congestive heart failure, coronary heart disease, diabetes, hypertension, stroke, and thyroid disease); self-reported cancer in lifetime (dichotomous); short index of cognitive function (continuous variable) based on seventeen questions about orientation, recall, and attention; self-reported health status (indicator variables for excellent/very good, good, 4/poor); dichotomous variables for self-reported use of medications that are bone-active (bisphosphonates) and bone-depleting (steroids); performance measures (continuous), including timed 8 ft walk,

repeated chair stands, and tandem stand timed; any self-reported activities of daily living (ADL) limitations (getting in and out of bed, eating, dressing) ; current smoking status (dichotomous measure based on self-report); and average use of alcohol per day in past year (continuous) .

3.7 ANALYSIS

Multiple methods of analysis were used to examine the relationship between overweight/obesity and osteoporosis/bone-related outcomes. Paper 1 was a cross-sectional analysis whereas Papers 2 and 3 were longitudinal analyses. The use of multiple types of analyses as well as multiple datasets provided the unique opportunity to describe the relationship between overweight/obesity and osteoporosis, bone loss, and hip fracture allowing for greater scope and applicability of study results.

3.7.1 PAPER 1

Bivariate analysis of study variables by BMI and BMD groups were conducted using F tests to determine if each BMI or BMD categories were significantly different from normal for continuous covariates and chi-square tests for significance were conducted for dichotomous covariates. Generalized linear regression models were used to examine the association between BMI and BMD, both measured continuously. Model 1 examined the unadjusted association between BMI and BMD. Model 2 added variables to control for demographics, socioeconomic status, physical function and activity, weight change, waist circumference, health status, medication and vitamin use, major depression, current smoking, and alcohol use. Models 3-5 examined potential effect

modification by adding interaction terms for BMI and age [continuous] (Model 3), BMI and sex (Model 4), and BMI and race [white vs non-white] (Model 5) to Model 2 variables. STATA 12 was used for all study analyses.

An example of the generalized linear regression model for Aim 1 is as follows:

$$Y_{BMD} = \beta_0 + \beta_1 X_1 + \beta_k X_k \ldots\ldots + e$$

Definitions for elements within model:

where Y_{BMD} = BMD of the femur (2005-2008); X_1 = BMI; β_0 = intercept or constant term; β = parameter to be estimated; X_k is the k^{th} covariate variable and β_k is the regression coefficient; e = error term

To account for the complex survey design and to make results representative of the US population, all analyses specified NHANES sampling design parameters. Using STATA Survey procedures, including a strata statement (sdmvstra), a cluster statement (sdmvpsu) and a weight statement (wtmec4yr) (National Center for Health Statistics, 2005). The sample weight chosen for this analysis comes from the mobile examination center (MEC) sample (subset of those interviewed in the survey) from which BMI and BMD data were obtained. This weight was chosen because it is recommended that the sample weight used for the analysis be obtained from smallest subpopulation for which data is being used (National Center for Health Statistics, 2005). Since two, 2-year cycles of NHANES are being used for analysis (2005-2006 and 2007-2008), a combined 4 year sample weight was constructed to represent the midpoint of the combined survey period (National Center for Health Statistics, 2005).

3.7.2 PAPER 2

The multivariable analysis utilized generalized estimating equations (GEE) to account for repeated observations and to predict rate of decline in BMD (femoral neck, hip, and whole body) over time (Year 1-6, Year 8, Year 10) by BMI. The first model predicted BMD (available observations from years 1-6, 8, and 10) by dummy variables for obesity and overweight (normal reference), a time variable, an interaction terms for obesity and time as well as overweight and time. This determines the direction of the association between BMI and BMD as well as the slope (rate of change) for each year by BMI group. The second (adjusted) model added control variables including age, site, income, education, physical activity level, calcium intake, vitamin D supplement use, lean muscle mass, fat mass, and weight change from age 50, depression, chronic conditions, self-reported health status, activities of daily living limitations, performance measure score, prescription medications, current smoking status, and alcohol use within the past year. Models 3-5 examined effect modifiers (age, sex, race, interactions with BMI categories) to see if the association between BMI and BMD is varied by these factors.

An example of the final generalized estimating equations regression model for Aim 2 is as follows:

$$Y_t = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 t + \beta_4 X_4 t + \beta_5 X_5 t \ldots + \beta_k X_k + \varepsilon$$

Definitions for elements within model:

where Y_t are BMD observations at time *t*, β_0 is the intercept, X_1 (obesity) and X_2 (overweight) are the independent variables , β_1 and β_2 are the regression coefficients for the independent variables (obesity/X_1 and overweight/X_2, respectively), *t* is time, β_3 is the regression coefficient for time, X_{4t} and X_{5t} are the interaction term variables (for obesity * time and overweight * time, respectively), β_4 and β_5 are the regression coefficients for the interaction terms (for obesity * time and overweight * time, respectively), X_k is the k^{th} covariate variable and β_k is the regression coefficient, and ε is the error.

Sensitivity analyses were also conducted to examine the association between baseline BMI and repeated measures of femoral neck BMD to determine if the significant obesity and time interaction was due to annual changes in weight (kg) over the study period.

3.7.3 PAPER 3

Tests of significance were used to determine if study covariates differed by hip fracture. F tests were used from generalized linear regression models for continuous covariates and chi-square tests of significance were used for categorical/dichotomous covariates. Cox proportional hazard ratios were used to examine if time to first event differs for overweight and obesity with normal BMI as the reference (Model 1). Model 2 controlled for the following confounders: age, income, education, marital status, low BMD, physical activity, calcium intake, vitamin D intake, prior hip fracture, fall frequency, activities of daily living limitations (ADLs), self-reported health status, chronic conditions, steroids and osteoporosis medications, cognitive function, smoking status and alcohol use. Models 3-5 examined age, sex, and race to determine if these

variables were effect modifiers between BMI categories (overweight and obese) and hip fracture.

An example of the final Cox proportional hazard ratio model for Aim 3 is as follows:

$$\log h(t) = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 \ldots\ldots \beta_k X_k + \varepsilon$$

Definitions for elements within model:

where log h(t) is the natural logarithm of the hazard function for hip fracture events , α is the baseline hazard function, X_1 is the independent variable for obesity, X_2 is the independent variable for overweight, X_3 is the independent variable for baseline BMD, X_4 is the interaction term for age and obesity, X_5 is the interaction term for a and overweight, X_k is the k^{th} mediator/covariate variable, β_1 through β_k are the regression coefficients, and ε is the error.

To account for the complex survey design and to make results representative of the US population, all analyses will specify NHANES sampling design parameters. Using SAS Survey procedures (only for phase 2 of the study), a strata statement (sdpstra2), a cluster statement (sdppsu2) and a weight statement (wtpfhx2) will be specified (National Center for Health Statistics, 1996). The sample weight chosen for this analysis comes from the mobile examination center (MEC) sample (subset of those interviewed in the survey) from which BMD data are obtained. This weight was chosen as it is recommended that the sample weight used for the analysis be obtained from smallest subpopulation for which data is being used.

CHAPTER 4. BODY MASS INDEX IS POSITIVELY ASSOCIATED WITH BONE MINERAL DENSITY IN US OLDER ADULTS[1]

4.1 ABSTRACT

Changes in the distribution of body mass index (BMI) over time have resulted in the majority of older adults being overweight or obese. Evidence regarding the relationship between body composition measures and bone mass is conflicting, possibly because different measures of obesity reflect multiple mechanisms. Specifically, there are important differences in the proportion of fat mass and risk of osteoporosis by age, sex, and race. The objective of this study is to examine the association between BMI and bone mineral density (BMD) in a recent, nationally representative sample of U.S. older adults as well as to see if this relationship varies by age, sex, and race. Data for this study were obtained from the National Health and Nutrition Examination Survey (2005-2008) for

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adults ages 50 and older (n=3,296). Linear regression models were used to predict BMD of the femoral neck (measured by DXA) as a function of BMI (measured height and weight) and a range of study covariates. BMI was positively associated with BMD ($p<0.001$), even after adjustment for an extensive set covariates. This relationship did not differ by age, sex, or race (i.e., interactions were not significant). Study results confirm the positive association between BMI and BMD and found the relationship does not differ by age, sex, and racial groups.

4.2 INTRODUCTION

Dramatic changes in the prevalence of obesity over time have resulted in the majority of older adults in the United States (US) having a high body mass index (BMI). Currently over 70% of older adults are either overweight or obese (Y. Wang & Beydoun, 2007), and this figure is expected to increase in the future(Y. Wang, Beydoun, Liang, Caballero, & Kumanyika, 2008). It is unknown how this upward shift in the BMI distribution has impacted the relationship between body composition and bone mass.

To date, studies examining the relationship between body composition and bone mass have found conflicting results(Beck et al., 2009; Greco et al., 2010; Lin et al., 2010; Nunez et al., 2007; Zhao et al., 2007). The majority of studies using BMI as an indicator of adiposity in US samples have primarily found obesity to be protective against osteoporosis(Albala et al., 1996; Asomaning et al., 2006; Beck et al., 2009; Siris et al., 2001) [although two studies using international samples found individuals with higher BMI levels to have higher odds of osteoporosis(Greco et al., 2010; Lin et al., 2010)]. However, numerous studies using direct measures of fat mass have found higher levels of

fat, particularly visceral fat, to be detrimental to bone mass(Bredella et al., 2010; Hsu et al., 2006; Nunez et al., 2007; Zhao et al., 2007). Additionally, overweight and obese individuals account for about half of all hip fractures compared to underweight older adults who account for 4% of hip fractures(Nielson et al., 2010). It remains unclear in the literature whether obesity is protective against osteoporosis, in part because results vary depending on the samples studied and measures used.

Inconsistent findings in the literature may also relate to variation across populations. Risk of osteoporosis increases with age(Albrand, Munoz, Sornay-Rendu, DuBoeuf, & Delmas, 2003b; Lips, 1997b), is higher in women than in men(Looker, Orwoll, Johnston, Lindsay, Wahner, Dunn, Calvo, Harris, & Heyse, 1997b), and is higher in whites than in blacks(Kessenich, 2000a; Peacock, Buckwalter, Persohn, Hangartner, Econs, & Hui, 2009a). Fat mass increases with age until about age 70, after which it remains stable or declines(Hughes et al., 2002; Kyle et al., 2001). Women tend to have a higher percentage of fat mass compared to men, but men tend to store more visceral fat compared to women(Blaak, 2001). White older adults also tend to have higher levels of visceral fat compared to African American older adults(Katzmarzyk et al., 2010). Previous research on the relationship between body composition and bone mass has been primarily conducted in white women, potentially ignoring important demographic differences in fat and bone mass.

This study examined variation in bone mineral density (BMD) across the BMI spectrum among older adults in a recent, nationally representative sample using data from the National Health and Nutrition Examination Survey (NHANES). Large samples sizes

available in NHANES data allowed for the examination of differences in the association between BMI and BMD by age, sex, and race.

4.3 MATERIALS AND METHODS

Data

NHANES is a cross-sectional survey of health and nutritional status that is designed to be representative of the U.S. non-institutionalized population, including an oversample of persons ages 60 and older, African Americans, and Hispanics(National Center for Health Statistics, 2007b). Participants take part in interviews and physical exams to provide a wide range of health-related data. This study used NHANES data from the 2005-2006 and 2007-2008 waves for persons 50 years of age and older.

Measures

NHANES provides body composition measures including measured height, weight, as well as measured BMD from dual energy x-ray absorptiometry (DXA). BMI was calculated as weight in kilograms divided by height in meters squared. A categorical BMI variable [normal (BMI: 18.50-24.99), overweight (BMI: 25.00-29.99) and obese (BMI: > 30.00)] was used in bivariate analyses to test the relationship between covariates and BMI groups. The sample excluded underweight individuals (BMI<18.50) as the inverse relationship between underweight and BMD is well understood(Ravn et al., 1999; Wardlaw, 1996). Additionally, the underweight represent only a small proportion of the older population (less than 2%). BMD was measured at the femoral neck in grams per centimeter squared. A categorical BMD variable [normal (BMD: >0.79 g/cm2 for men

and >0.74 g/cm2 for women, corresponding to a T score of -1 or higher); osteopenia (BMD: >0.59 and <0.79 g/cm2 for men and >0.56 and <0.74 g/cm2 for women, corresponding to a T-score between -1 and -2.5); osteoporosis (BMD: <0.59 g/cm2 for men and <0.56 g/cm2 for women, corresponding to a T-score lower than -2.5)](Looker, Orwoll, Johnston, Lindsay, Wahner, Dunn, Calvo, Harris, & Heyse, 1997b) was used in bivariate analyses to test the relationship between covariates and BMD groups.

Demographic factors were self-reported and included age, sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American), poverty income ratio (a ratio of family income to poverty threshold, 0-5, missing values were imputed based on the sample mean), education (<9th grade, 9-11 grade, 12th grade completed, some college completed, college graduate), and marital status (married versus widowed/divorced/separated/single).

Common risk factors for osteoporosis were examined, including physical activity, health status, weight change, bone-related vitamin and medication use, depression, current smoking status, and average alcohol use in the past year. Physical activity in the past 30 days was measured by three dichotomous variables: walking or biking for transportation, moderate physical activity, and vigorous physical activity. Changes to the phrasing of the physical activity questions between the study time periods (2005-2006 and 2007-2008) may have contributed to variation in frequencies of physical activity across study years (21% reported walking or biking for transportation in 2005-2006 compared to 19% in 2007-2008; 43% reported moderate physical activity in 2005-2006 compared to 35% in 2007-2008; and 15% reported vigorous activity in 2005-2006 compared to 11% in 2007-2008). Despite these differences, the physical activity content

was conceptually similar, and these variables were included to attempt to account for physical activity as a possible confounder. Weight change (pounds) was calculated as change from self-reported greatest lifetime weight to measured weight. Measured waist circumference (cm), a measure of abdominal fat, was characterized as a dichotomous variable indicating high waist circumference for bivariate analyses (corresponding to a waist circumference of 102 cm or higher for men and 88 cm or higher for women)(Koster et al., 2008). Health status included any activities of daily living (ADL) limitations (any difficulty dressing, getting in and out of bed, and eating), self-reported general health status (excellent, very good, and good versus fair or poor), chronic conditions (cardiovascular disease, diabetes, thyroid disease, and cancer), and major depression (Patient Health Questionnaire-9, score of 9 or more). Bone-related vitamin and medication use included self-reported use (yes/no) of calcium supplements, vitamin D supplements, bisphosphonates, and steroids. A dichotomous variable was created for current smoking status (some everyday or some days versus not at all). A continuous measure was used for average alcohol use (days) within the past year.

Sample

Of the 5,288 NHANES participants aged 50 years and older, 1,271 were removed from the sample due to missing BMD, 25 were removed due to missing BMI and an additional 59 were removed who were underweight. Almost 30% of obese individuals were missing BMD measurement, compared to 12%-13% of normal weight and overweight participants ($p<0.001$). An additional 637 individuals were excluded from the sample due to missing data on study covariates, leaving a final analytic sample of 3,296.

4.4 ANALYSIS

Tests of significance to determine if study covariates differed by BMI category (Table 4-1) or BMD category (Table 4-2) utilized F tests from generalized linear regression models for continuous covariates and chi-square tests for categorical/ dichotomous covariates.

Generalized linear regression models were used to examine the association between BMI and BMD, both measured continuously. Model 1 examined the unadjusted association between BMI and BMD. Model 2 added variables to control for demographics, socioeconomic status, physical function and activity, weight change, health status, medication and vitamin use, major depression, current smoking, and alcohol use. Models 3-5 examined potential effect modification by adding interaction terms for BMI and age [continuous] (Model 3), BMI and sex (Model 4), and BMI and race [white vs non-white] (Model 5) to Model 2 variables. All data analyses used NHANES sample weights and sampling design parameters to account for the complex study design. STATA 12 was used for all study analyses.

4.5 RESULTS

Table 4-1 displays the bivariate relationships between study covariates and BMI groups. The correlation between BMI and BMD was 0.40. There was a monotonic increase in mean BMD across BMI groups (p for trend <0.001). Obese older adults had a lower prevalence of osteopenia and osteoporosis, a lower mean age, a lower proportion of non-Hispanic white participants, the lowest physical activity, lowest weight change since

greatest lifetime weight, and the lowest prevalence of current smokers, vitamin D use, and bisphosphonate use, and the lowest alcohol use in the past year ($p<0.05$). The obese group had the highest proportion with diabetes and cardiovascular disease ($p<0.05$).

Table 4-1. Sample Characteristics by Body Mass Index, 2005-2008, n=3,296

	Normal	Overweight	Obese	P-value
	n=882	n=1,300	n=1,114	
Bone mineral density of femoral neck (gm/cm^2), mean (SD)	0.701 (0.114)	0.775 (0.128)	0.837 (0.136)	<0.001
Bone mineral density categories (%)†				<0.001
Normal	27.9	48.6	70.6	
Osteopenia	60.8	47.9	27.9	
Osteoporosis	11.4	3.5	1.6	
High waist circumference (%)	16.2	68.2	98.8	<0.001
Age in years, mean (SD)	63.7 (10.4)	63.6 (9.9)	61.3 (8.9)	<0.001
Female (%)	63.0	43.9	49.7	<0.001
Non-Hispanic White (%)	88.9	87.1	83.1	<0.001
Poverty income ratio, mean (SD)*	3.3 (1.5)	3.3 (1.5)	3.3 (1.5)	0.634
Education in years, (%)				0.461
< 9^{th} grade	6.4	7.5	6.8	
9-11^{th} grade	11.9	10.4	12.3	
12^{th} grade completed	27.2	28.2	26.9	
Some college	26.2	27.1	30.4	
College completed	28.3	26.8	23.6	
Married (%)	61.4	65.4	67.8	0.089
Walk or bike for transportation (%)	23.6	22.0	16.3	0.006
Moderate physical activity (%)	51.7	51.4	44.2	0.032
Vigorous physical activity (%)	22.7	20.1	16.7	0.052
Weight change (lbs) since greatest lifetime weight, mean (SD)	-18.8 (23.4)	-14.7 (19.0)	-12.0 (21.5)	<0.001
Activities of daily living limitations (%)	3.3	3.5	3.2	0.929
Excellent-good health (%)	83.8	84.8	79.0	0.009
Cardiovascular disease (%)	11.6	16.0	16.6	0.020
Diabetes (%)	6.3	9.3	21.1	<0.001
Thyroid disease (%)	16.4	13.9	16.4	0.356
Cancer (%)	17.6	17.0	15.2	0.425
Major Depression (%)	5.7	6.6	8.4	0.115
Calcium use, (%)	44.0	36.7	37.5	0.049
Vitamin D use, (%)	40.9	33.1	32.0	0.003

Table 4-1 Continued

Bisphosphonate use (%)	11.1	3.6	1.9	<0.001
Steroid use (%)	11.7	7.3	7.7	0.015
Current smoker (%)	26.5	14.7	12.9	<0.001
Days used alcohol in past year, mean (SD)	21.8 (45.1)	16.1 (34.1)	11.0 (20.7)	<0.001

* Poverty income ratio was imputed based on the mean of the observed sample (N=3,058).
† BMD categories defined using a young, sex specific mean (normal BMD: T score of - 1 or higher, osteopenia: T score between -1 and -2.5, osteoporosis: T score –of -2.5 or lower)(Looker, Orwoll, Johnston, Lindsay, Wahner, Dunn, Calvo, Harris, & Heyse, 1997b)

Table 4-2 displays the bivariate relationship between study covariates and BMD groups. The osteoporotic group had the lowest mean BMI and poverty income ratio. They were also less likely to report excellent-good health, to have completed 12 years of education or more, to be married, and to report moderate or vigorous physical activity ($p<0.01$). The osteoporotic group also had the highest mean age and the highest proportion of non-Hispanic whites, females, cardiovascular disease, major depression, and bisphosphonate use ($p<0.05$).

Table 4-2. Sample Characteristics by Bone Mineral Density, 2005-2008, n=3,296

	Normal	Osteopenia	Osteoporosis	P- value
	n=1,649	n=1,465	n=182	
Body mass index (kg/m^2), mean (SD)	30.2 (5.3)	26.8 (4.5)	24.4 (4.2)	<0.001
High waist circumference (%)	74.1	55.2	39.9	<0.001
Age in years, mean (SD)	60.2 (8.6)	64.8 (9.9)	71.6 (11.2)	<0.001
Female (%)	45.7	55.1	70.0	<0.001
Race (%)				<0.001
Non-Hispanic White	82.0	90.3	93.5	
Non-Hispanic Black	13.1	5.3	3.4	
Mexican American	5.0	4.4	3.2	
Poverty income ratio, mean (SD)*	3.5 (1.5)	3.2 (1.5)	2.4 (1.4)	<0.001
Education in years, (%)				0.013
< 9th grade	6.3	7.5	9.3	
9-11th grade	10.8	11.2	19.2	
12th grade completed	26.7	28.3	28.7	
Some college	29.8	25.8	29.8	
College completed	26.5	27.2	13.1	

Married (%)	68.0	64.5	41.7	<0.001

Table 4-2 Continued

Walk or bike for transportation (%)	20.5	20.7	19.1	0.881
Moderate physical activity (%)	49.3	50.3	36.5	0.005
Vigorous physical activity (%)	22.1	18.3	7.6	0.009
Weight change (lbs) since greatest lifetime weight, mean (SD)	-14.3 (20.6)	-15.3 (21.8)	-18.1 (22.7)	0.109
Activities of daily living limitations (%)	2.9	3.3	8.6	<0.001
Excellent-good health (%)	82.9	83.7	70.2	<0.001
Cardiovascular disease (%)	13.5	15.2	28.0	0.003
Diabetes (%)	14.1	10.4	12.6	0.013
Thyroid disease (%)	15.1	14.8	23.4	0.085
Cancer (%)	13.7	19.4	19.8	<0.001
Major Depression (%)	7.0	6.2	13.5	0.012
Calcium use (%)	37.3	41.0	37.7	0.118
Vitamin D use (%)	33.0	36.9	36.2	0.147
Bisphosphonate use (%)	1.5	8.1	14.2	<0.001
Steroid use (%)	8.7	8.9	5.9	0.427
Current smoker (%)	17.8	16.3	23.3	0.097
Days used alcohol in past year, mean (SD)	15.5 (31.5)	17.5 (38.5)	7.4 (18.9)	0.607

* Poverty income ratio was imputed based on the mean of the observed sample (N=3,058).

Results for the main analysis are displayed in Table 4-3. BMI was significantly positively associated with BMD in the unadjusted model (Model 1), and this did not change with the addition of covariates to Model 2 ($p<0.001$). Controlling for covariates, every unit increase in BMI was associated with a 0.0082 g/cm^2 increase in BMD.

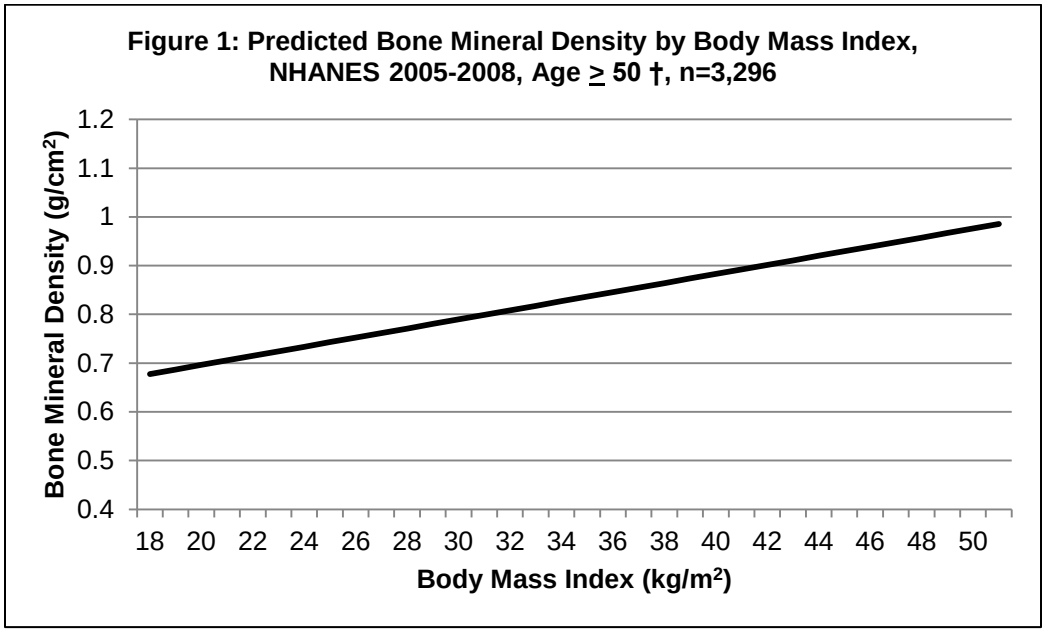
Interaction terms for BMI and age (p=0.345), BMI and sex (p=0.413), and BMI and race (p=0.725) were not statistically significant. Figure 4-1 displays the positive relationship between BMI and BMD. Predicted mean BMD increases as BMI increases.

Table 4-3. Generalized Linear Regression Models Predicting Bone Mineral Density (g/cm^2) by Body Mass Index (kg/m^2), 2005-2008, n=3,296

	b	SE	P value
Model 1: Unadjusted			
BMI	.0106	.0004	<0.001
Model 2: Covariates†			
BMI	.0082	.0010	<0.001
Model 3: Age Interaction†			
BMI	.0105	.0030	0.002
BMI * age	-.0000	.0000	0.345
Model 4: Sex Interaction†			
BMI	.0088	.0012	<0.001
BMI * female	-.0009	.0010	0.413
Model 5: Race Interaction†			
BMI	.0078	.0012	<0.001
BMI * white	.0004	.0012	0.725

† Controlling for age, sex, race, poverty income ratio, education, marital status, physical activity, activities of daily living limitations, weight change, waist circumference, self-reported health, chronic disease, calcium & vitamin D use, bisphosphonate & steroid use, depression, smoking status, and alcohol use.

Figure 4-1: Predicted Bone Mineral Density by Body Mass Index, NHANES 2005-2008, Age ≥ 50 †, n=3,296



† Controlling for age, sex, race, poverty income ratio, education, marital status, physical activity, activities of daily living limitations, weight change, waist circumference, self-reported health, chronic disease, calcium & vitamin D use, bisphosphonate & steroid use, depression, smoking status, and alcohol use.

4.6 DISCUSSION

This study confirms the positive association between BMI and BMD in a recent, nationally representative sample of older adults, controlling for an extensive set of covariates. This relationship did not differ by age, sex, or race.

BMI is commonly used as a clinical measure for assessing risk of fracture(J. Compston et al., 2009; De Laet et al., 2005; Kanis et al., 2005; Kanis & Reginster, 2008), particularly in the absence of BMD. BMI is an effective measure for capturing the weight-bearing aspect of a heavier load on the skeleton(Beck et al., 2009; Reid et al., 1992), but is not ideal for characterizing fat mass or fat distribution(Reid et al., 1994; Zhao et al., 2007). Measures of body composition that are more indicative of fat distribution have found different outcomes related to bone mass(Sheu & Cauley, 2011). Because visceral fat is detrimental to bone mass, obese individuals with higher composition of visceral fat may not be protected by their extra fat(Blaak, 2001; Sheu & Cauley, 2011). Multiple measures of body composition may be useful in understanding how obesity relates to bone mass and reconciling inconsistent findings in the literature. For example, some studies have found both a positive association between weight/BMI and bone mass and a negative relationship between fat and bone mass within a given weight/BMI category(Hsu et al., 2006; Zhao et al., 2007). These results indicate two diverging aspects of obesity on bone mass (e.g. the positive weight-bearing of a heavier load and the detrimental aspects associated with fat mass). Studies examining the relationship between BMI and BMD should consider operationalizing obesity with multiple measures to account for potentially diverging impacts on bone mass.

Previous other studies have demonstrated that the composition of fat mass impacts the BMI and BMD relationship. For example, visceral fat is associated with higher levels of proinflammatory cytokines that promote bone resorption and osteoporosis, while subcutaneous fat is associated with higher levels of proteins and hormones (estrogren, adiponectin, leptin) that protect from osteoporosis(Blaak, 2001; Sheu & Cauley, 2011). Fat measured two-dimensionally (with DXA) or with surrogate measures (waist circumference, BMI, weight) can not distinguish between the composition of fat mass (Sheu & Cauley, 2011). Measures that differentiate the type of fat (e.g. CT scans) may be necessary to understand the complex relationship between obesity and osteoporosis(Sheu & Cauley, 2011).

Even though important differences in fat and bone mass exist across demographic groups, this study did not find the relationship between BMI and BMD to vary by age, sex, or race. Many previous studies have found obesity to be protective against osteoporosis in postmenopausal women(Albala et al., 1996; Asomaning et al., 2006; Beck et al., 2009; Looker et al., 2007; Siris et al., 2001). This study extends this work by examining the BMI and BMD relationship in a representative sample of older adults to confirm this association in the context of sex differences. Although osteoporosis is predominately found among postmenopausal women, there is a growing public health concern related to osteoporosis and fracture among older men(Khosla, Amin, & Orwoll, 2008). Previous studies have found race to be a significant effect modifier of the BMI and BMD association, but only among postmenopausal women. Looker et al.(Looker et al., 2007), using earlier NHANES data, found a significant race and overweight (including obese) interaction predicting the prevalence of osteoporosis in postmenopausal women,

but did not find a significant age interaction, similar to the current study. Castro et al.(Castro et al., 2005), using data from 2 medical centers in New York, found that obese white women were protected against osteoporosis but obese African American women had higher odds of osteoporosis. While the current study did not find significant race differences in the BMI and BMD relationship, it is possible that the inclusion of men in the sample masked important race and sex variations in the BMI and BMD relationship. Sensitivity analysis (data not shown) found a significant three way interaction between BMI, race, and sex, but this was not accompanied by significant BMI and race interactions in analyses stratified by sex.

Results from this study shed light on the conflicting literature on body composition and bone mass by confirming that BMI is positively associated with BMD. What remains unclear is whether a higher BMI translates into protection against fracture. Even though obesity is protective against osteoporosis, studies have found that obese, compared to normal weight older adults, are at a higher risk for falls()(Himes & Reynolds, 2011) and fractures(Nielson et al., 2010). It is possible that the relationship between BMD and fracture may differ by BMI. Among obese who fracture, most do so with normal BMD(Premaor et al., 2010). Therefore, low BMD as a marker for fracture risk may be less meaningful among obese individuals. Additionally, bone quality and strength may be more useful in predicting risk of fracture than BMD alone. For example, when accounting for body size, obese women have less relative bone strength than their normal weight counterparts(Beck et al., 2009).

This study has limitations that should be considered when interpreting results. The study design is cross-sectional, and therefore findings can not establish temporal

relationships or causality. Another potential limitation was the higher proportion of obese individuals missing on the study outcome (BMD). NHANES restricts DXA measurements for individuals over 300 pounds(National Center for Health Statistics, 2007a)due to measurement limitations of the scanning area on DXA machines(Tataranni & Ravussin, 1995). However, sensitivity analysis modeling weighting estimating equations(Shardell et al., 2011) (which used NHANES survey weights multiplied by the inverse probability of being observed) confirmed the positive association between BMI and BMD (results not shown). As the prevalence of obesity continues to rise among older adults, weight limits for DXA machines may create measurement issues for future research in this area.

This study had a number of strengths, including the nationally representative, large sample size that provides population-based estimates and allows for examination of potential effect modifiers. Additionally, NHANES includes a rich set of measures to examine body composition and bone mass, as well as an extensive set of covariates.

Overall, BMI was found to be positively associated with BMD in a nationally representative sample of older adults. This relationship did not differ by age, sex, or race. Further research is needed to understand the relationship between obesity and risk of fracture. Understanding the relationship between body composition, bone mass, and fracture is particularly important in light of the increasing prevalence of obesity among older adults.

CHAPTER 5. CHANGES IN BONE MINERAL DENSITY OVER TIME BY BODY MASS INDEX IN THE HEALTH ABC STUDY[2]

5.1 ABSTRACT

Cross-sectional studies have found a positive association between body mass index (BMI) and bone mineral density (BMD), but little is known about the longitudinal relationship in US older adults. We examined average annual rate of change in BMD by baseline BMI in the Health, Aging, and Body Composition Study. Repeated measurement

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of BMD was performed with dual energy absorptiometry (DXA) at baseline, and years 3, 5, 6, 8, 10. Multivariable generalized estimating equations were used to predict mean BMD (femoral neck, total hip, and whole body) by baseline BMI group, adjusting for covariates. The sample included 2,570 subjects of whom 43% were overweight and 24% were obese with a mean baseline femoral neck BMD of 0.743 g/cm^2, hip BMD of 0.888 g/cm^2, and whole body BMD of 1.09 g/cm^2. There were no significant differences between BMI groups for change in total hip or whole body BMD over time. However, there were significant differences between BMI groups for change in femoral neck BMD over time ($p<0.001$). Obese older adults lost 0.002 g/cm^2 of BMD per year more compared with normal weight older adults ($p<0.001$). Femoral neck BMD change over time did not differ between the overweight and normal weight BMI groups ($p=0.74$). This relationship did not change in sensitivity analysis controlling for annual weight change over the study period. Obese older adults had the highest mean femoral neck BMD at baseline but had the lowest mean BMD by year 10. In year 10, adjusted femoral neck BMD ranged from 0.696 g/cm^2 among obese, 0.709 g/cm^2 among normal weight, and 0.719 g/cm^2 among overweight older adults. Findings underscore the importance of looking at the longitudinal relationship between body composition and bone mineral density among older adults, indicating that high body mass may not be protective for bone loss over time.

5.2 INTRODUCTION

Numerous studies have found a strong, cross-sectional association between body mass index (BMI) and bone mineral density (BMD)(Albala et al., 1996; Asomaning et al., 2006; Beck et al., 2009), but little is known about the longitudinal relationship in the

US population. Many studies have found obesity to be protective against bone loss, but the majority have been conducted in non-US populations(Burger et al., 1998; Holecki et al., 2012; Jones, Nguyen, Sambrook, Kelly, & Eisman, 1994; Ribot et al., 1994; Saarelainen et al., 2012; Tremollieres, Pouilles, & Ribot, 1993) whose cultural differences in exercise and diets, as well as dramatic differences in the prevalence of obesity, make results difficult to generalize to US older adults. Ravn et al.(Ravn et al., 1999) examined this association in a US sample in the 1990s, but these results do not reflect dramatic increases in the prevalence of obesity(Ding et al., 2007; Flegal et al., 2010) and the development of obesity at younger ages among more recent birth cohorts of older adults(Leveille et al., 2005). Additionally, most research on the association between BMI and bone loss has focused on underweight older adults, who are at the highest risk for bone loss and fracture(Burger et al., 1998). However, underweight individuals represent a small proportion of the total older adult population (around 2%)(Flegal, Graubard, Williamson, & Gail, 2005). Dramatic increases in the prevalence of overweight and obesity in the US necessitate a focus on heavier individuals, who make up the majority of the older adult population(Cao, 2011).

The objective of this study was to examine change in BMD of the femoral neck, total hip, and whole body over time (10 years) by baseline BMI categories among a recent cohort of US older adults. Using data from the Health, Aging, and Body Composition Study (Health ABC), this analysis was able to control for an extensive set of potential confounding variables associated with bone loss and obesity.

5.3 MATERIALS AND METHODS

Study sample

The Health ABC study follows a healthy cohort of 3,075 White and Black well-functioning men and women (age 70-79 at enrollment in 1997-1998) from two US field centers (Pittsburgh, PA and Memphis, TN). Participants in designated zip codes near the two field centers were recruited using a random sample of White Medicare beneficiaries and all age-eligible Black community residents. Only individuals who were disability and cancer free at baseline were eligible to be enrolled in the study. Ten years of longitudinal follow-up data are available for the baseline sample. The final analytic sample not missing on baseline study variables was N=2,570. Variables with large amounts of missing data included percent weight change from age 50 to baseline (n=105), total fat free and total fat mass (n=106), and performance measures (n=95), and prevalence of cardiovascular disease (n=56) and stroke (n=29).

Body mass index

BMI categories were calculated by measured height and weight at baseline (weight in kilograms divided by height in meters squared). BMI categories ranged from 18.5 to 24.9 for normal weight (reference), 25.0 to 29.9 for overweight, and $\geq$ 30.0 for obese. Underweight individuals were excluded from all analyses (n=25). Baseline BMI was used to determine if body mass prior to age 80 (at ideal age for bone loss interventions as risk of hip fracture greatly increases after age 80(Looker et al., 2010) was an independent predictor of bone loss over time. Prior studies have found weight change (particularly weight loss) to be highly associated with bone loss(Beck et al., 2001; Cauley

et al., 2005)(). However, this study focused on a population who were either overweight or obese for most of their older adult lives (evident in % weight change since age 50 in Table 5-1). The constant, biomechanical loading of these higher body mass categories would have been present throughout the older age of this sample. Therefore, this study was able to examine the independent impact of overweight and obesity in older age and the impact of these BMI categories on bone loss.

Femoral neck, total hip, and whole body bone mineral density

The outcome variables include repeated measures of femoral neck, total hip, and whole body BMD. Femoral neck and total hip BMD were measured at baseline, year 3, year 5, year 8, and year 10. Whole body BMD was measured annually from baseline to year 5 and again at years 8 and 10. BMD was obtained from dual energy absorptiometry (DXA) measurements and measured in units of g/cm^2. A number of participants were missing follow-up data for femoral neck, total hip, and whole body DXA (386 people were missing DXA data in year 3 and 1355 were missing in year 10).

Potential confounders

A number of baseline variables were included in regression models to see if they accounted for the association between baseline BMI and change in BMD. Education (less than high school, high school graduate, post-secondary [reference]) was included in the analyses as a proxy for socioeconomic status. Health status indicators included physical performance measures based on the Short Physical Performance Battery (range 0-4),

prevalence of chronic conditions via clinical data, self-report, or medications [diabetes, cardiovascular disease]; self-report or medications [hypertension, cancer]; or self-report only [stroke], self-reported health status (good or fair/poor [reference]), depression measured by the Center for Epidemiologic Studies Depression Scale (CESD, range 0-100), and cognition based on the Modified Mini-Mental State examination (3MS, range 0-20). Factors related to both obesity and bone loss included bone-active medications (bisphosphonates and steroids), physical activity (kcal/week walking and exercise), vitamin D and calcium supplement intake, percent weight change from age 50, smoking status, and frequent alcohol use. A dummy variable indicating Memphis Health ABC site (Tennessee reference) was also included in the regression analysis to account for residual differences across study sites.

Statistical analysis

Descriptive statistics were used to compare study characteristics at baseline by BMI categories. Tests of significance utilized chi-square tests and generalized linear regressions for dichotomous and continuous variables, respectively. Generalized estimating equations were used to examine the association between baseline BMI categories and repeated measures of BMD [femoral neck, total hip, and whole body]. Models predicted BMD by obesity and overweight (normal weight reference), time, interaction terms for obesity and time and overweight and time (to determine the direction of the association and slope between BMI categories and BMD) in an unadjusted model as well as a model adjusted for covariates listed in Table 5-1.

Sensitivity analyses were also conducted to examine whether significant associations between baseline BMI and repeated measures of BMD could be accounted for by annual changes in weight (kg) over the study period or by demographic (age, race [white or black (reference)], and gender) differences in the rate of BMD decline. Adjusted per year change in BMD by baseline BMI categories are presented by gender as there are important differences between men and women in the prevalence of overweight and obesity as well as bone-related outcomes such as bone-loss and fracture. Sensitivity analyses also added total fat free mass (gm) and total fat mass (gm) to the adjusted models to see if results changed when accounted for body composition at baseline.

5.4 RESULTS

The sample included 2,570 subjects of whom 43% were overweight and 24% were obese [Table 5-1]. The sample had a mean baseline femoral neck BMD of 0.743 g/cm^2 (SD=0.142), a mean total hip BMD of 0.888 g/cm^2 (SD=0.169), and a mean whole body BMD of 1.09 g/cm^2 (SD=0.141). There were no significant differences in missing femoral neck or total hip BMD by BMI category. However, there were significant differences in missing whole body BMD by BMI category in year 3 and 8 with the overweight participants having a higher proportion of missing whole body DXAs than normal or obese participants.

Table 5-1. Sample Characteristics at Baseline by Body Mass Index Categories, n=2,570					
	Total	Normal	Overweight	Obese	p-value
N	2,570	852	1,095	623	
Bone mineral density g/cm^2 [mean (SD)]					
Whole Body	1.090 (0.141)	1.058 (0.142)	1.099 (0.141)	1.116 (0.134)	<0.001
Total Hip	0.888 (0.169)	0.808 (0.160)	0.904 (0.158)	0.968 (0.153)	<0.001
Femoral Neck	0.743 (0.142)	0.683 (0.135)	0.750 (0.132)	0.814 (0.135)	<0.001
Age [mean (SD)]	73.6 (2.9)	73.9 (2.9)	73.6 (2.9)	73.1 (2.8)	<0.001
Female %	50.8	53.5	45.0	57.3	<0.001
Black %	39.7	32.2	35.9	56.7	<0.001
Education					0.001
< High school	23.9	21.4	22.7	29.5	
High school grad	32.1	29.0	32.7	35.3	
Post-secondary	44.0	49.7	44.6	35.2	
Percent weight change from age 50 [mean (SD)]	6.3 (14.0)	-1.6 (9.9)	6.0 (11.8)	17.3 (15.0)	<0.001
Vitamin D use %	8.4	11.5	7.6	5.6	<0.001
Calcium use %	18.4	24.1	17.1	13.2	<0.001
Physical activity, kcal/week [mean (SD)]	1081.8 (1904.4)	1,044.7 (1951.8)	1,216.6 (2037.0)	895.4 (1549.3)	0.233
Total fat free mass, gm [mean (SD)]	48,981.3 (10,407.5)	43,632.5 (8,744.0)	50,001.3 (9,556.9)	54,503.2 (10,514.8)	<0.001
Total fat mass, gm [mean (SD)]	26,562.2 (8,474.5)	19,114.1 (4,124.0)	26,377.2 (4,547.7)	37,073.1 (7,090.1)	<0.001
Diabetes %	14.5	9.0	14.5	22.0	<0.001
Cardiovascular disease %	24.6	23.1	26.1	23.9	0.283
Hypertension %	43.7	34.6	43.0	57.3	<0.001
Cancer %	19.2	18.8	19.9	18.6	0.746
Stroke %	1.1	0.7	1.7	0.3	0.011
Good health %	84.8	85.7	86.8	79.9	<0.001
Steroid use %	2.3	2.6	2.1	1.9	0.602
Bisphosphonate use %	4.0	6.3	3.1	2.3	<0.001
Performance measures, 0-4 [mean (SD)]	2.2 (0.5)	2.3 (0.5)	2.3 (0.5)	2.0 (0.6)	<0.001
Cognition (3MS), 0-100 [mean (SD)]	90.6 (7.8)	90.7 (8.3)	90.9 (7.6)	89.8 (7.6)	0.007
CESD score, 0-20 [mean (SD)]	4.6 (5.2)	4.7 (5.1)	4.6(5.2)	4.5 (5.2)	0.433
Smoking status %	9.8	14.8	8.1	6.1	<0.001
Frequent drinking %	29.5	36.2	31.1	23.0	<0.001

Obese older adults had the highest mean femoral neck ($p<0.001$) and total hip ($p<0.001$) BMD and whole body BMD ($p<0.001$) at baseline compared to normal weight older adults [Table 5-1]. Obese older adults were more likely to be younger, female, black, less educated, gained more weight since age 50, had more fat free and fat mass, and were more likely to have diabetes or hypertension. Obese older adults were less likely to use vitamin D or calcium supplements or bisphosphonate uses, less likely to have good health, functional performance, cognition, and less likely to smoke or drink frequently.

Table 5-2 displays the unadjusted and adjusted baseline BMD (femoral neck, hip, and whole body) by BMI category from multivariable analyses utilizing generalized estimating equations. There was a significant BMI group by time interaction ($p<0.001$) for femoral neck BMD. Obese older adults lost 0.002 g/cm^2 of femoral neck BMD per year more compared with normal weight older adults ($p<0.001$) for a total mean loss of 0.02 g/cm^2 over the study period. Femoral neck BMD change over time did not differ between the overweight and normal weight BMI groups ($p=0.75$). There were no significant differences in total hip and whole body BMD over time by BMI group.

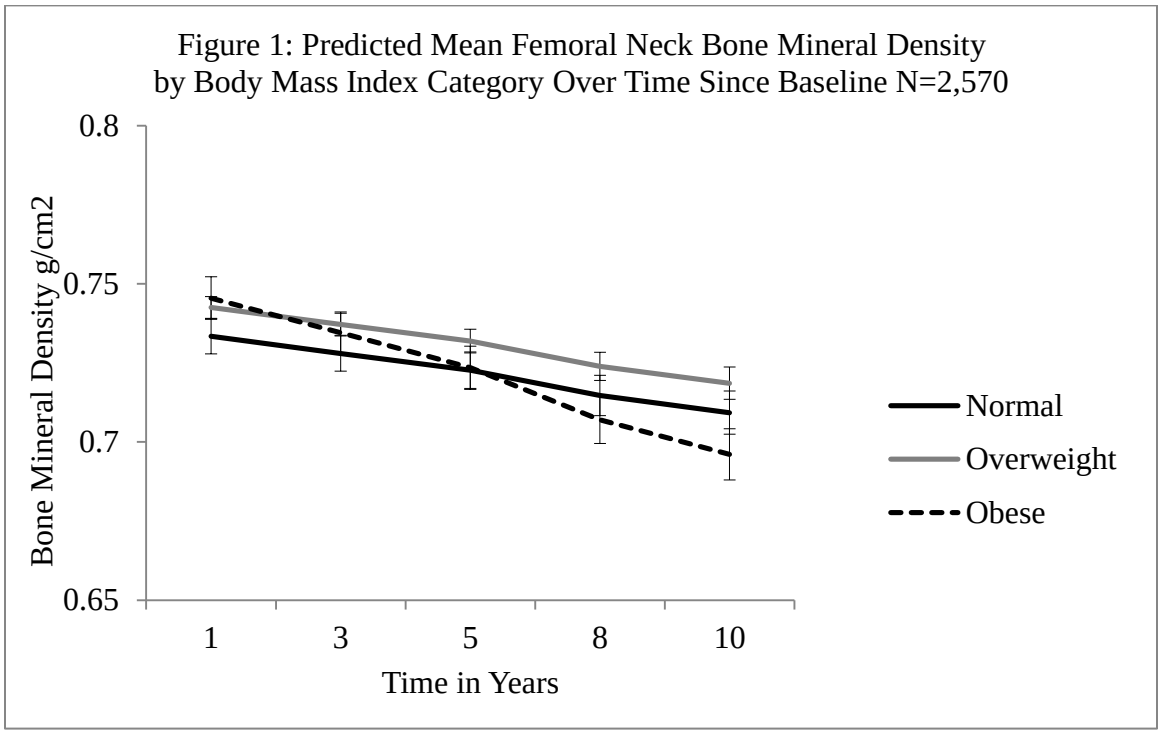
Table 5-2. Unadjusted and Adjusted Change in BMD by Body Mass Index Category, n=2,570†

	Femoral Neck		Total Hip		Whole Body	
	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value
Unadjusted Results						
Overweight	0.0692	<0.0001	0.0989	<0.0001	0.0441	<0.0001
Obesity	0.1352	<0.0001	0.1679	<0.0001	0.0615	<0.0001
Time	-0.0032	<0.0001	-0.0039	<0.0001	-0.0027	<0.0001
Overweight * Time	0.0002	0.7482	0.0003	0.7580	-0.0003	0.6789
Obesity * Time	-0.0026	0.0032	-0.0011	0.2573	-0.0005	0.5715
Adjusted Results						
Overweight	0.0479	<0.001	0.0655	<0.0001	0.0240	<0.0001
Obesity	0.1031	<0.0001	0.1322	<0.0001	0.0540	<0.0001
Time	-0.0026	<0.001	-0.0035	<0.0001	-0.0023	<0.0001
Overweight * Time	0.0000	0.9887	0.0000	0.9916	-0.0004	0.5279
Obesity * Time	-0.0029	0.0003	-0.0015	0.0652	-0.0008	0.3250

† BMD= Bone mineral density

Compared to normal weight older adults, obese older adults had the highest predicted mean femoral neck BMD at baseline ($p<0.001$) but had the lowest predicted mean femoral neck BMD by year 10 ($p<0.001$). In year 10, obese older adults had a mean femoral neck BMD of 0.696 g/cm^2 (SE=0.008), overweight older adults had a mean of 0.709 g/cm^2 (SE=0.007), and normal weight older adults had a mean femoral neck BMD of 0.719 g/cm^2 (SE=0.005) [Figure 5-1], however mean BMD values for the obese ($p=0.26$) and overweight ($p=0.27$) groups were not statistically different than the normal weight group at year 10.

Figure 5-1.Predicted Mean Femoral Neck Bone Mineral Density by Body Mass Index Category Over Time N=2,570†



†Adjusted for age, sex, race, education, physical performance measures, diabetes, cardiovascular disease, hypertension, cancer, stroke, self-reported health status, depression, cognition, bone-active medications, physical activity, vitamin D and calcium supplement intake, percent weight change from age 50, smoking status, frequent alcohol use, and Health ABC site.

A number of sensitivity analyses were conducted to see if study results remained after accounting for demographic factors. For femoral neck BMD, significant interactions with time were observed for sex and race, but not age. However, the addition of these interaction terms did not account for the significant obesity and time interaction. For femoral neck BMD, significant interactions with time were observed for gender with time (p=0.045) and white race (p=0.009). For total hip BMD, the interaction term for white race and time (p=0.014) was significant [the interaction between gender and time was approaching significance (p=0.071)]. For whole body BMD, there were no significant interactions between time and demographic factors (age, gender, or race).

Sensitivity analyses also examined additional body composition variables as confounders as well as weight change over time. There were also no differences in study results when body composition (baseline lean muscle mass and fat free mass [continuous variables, gm units]) variables were added to the adjusted models. Annual weight change (kg) over the study period (mean= -1.28) was significantly associated with change in femoral neck BMD over time (p= 0.003), but did not change the significant obesity and time interaction.

Adjusted per year change in femoral neck BMD by BMI category is presented in Table 5-3 to display differences in gender and race and to further explore the significant loss in femoral neck BMD found among obese older adults. It appears that overweight and obese men lose slightly more femoral neck BMD annually compared to overweight and obese women, respectively. Additionally, Black older adults who are normal weight or obese lose more femoral neck BMD than their White BMI category counterparts.

Table 5-3. Adjusted Per Year Change in Femoral Neck BMD by Baseline BMI Category, Gender, and Race, n=2,570†

BMI Category	**Gender**		**Race**	
	Women	Men	White	Black
Normal	-0.003	-0.003	-0.002	-0.005
Overweight	-0.002	-0.003	-0.003	-0.003
Obese	-0.005	-0.006	-0.005	-0.006

†BMD= Bone mineral density (g/cm^2), BMI=Body mass index (kg/m^2); Adjusted for age, education, physical performance measures, diabetes, cardiovascular disease, hypertension, cancer, stroke, self-reported health status, depression, cognition, bone-active medications, physical activity, vitamin D and calcium supplement intake, percent weight change from age 50, smoking status, frequent alcohol use, and Health ABC site. Significant interactions between female gender with time (p=0.045) and white race (p=0.009) with time in predicting femoral neck BMD.

5.5 DISCUSSION

In summary, this study found significant differences in femoral neck BMD over time by BMI group but did not find differences in total hip or whole body BMD over time. Compared to normal weight older adults, obese older adults had higher mean femoral neck BMD at baseline but had lower mean BMD by year 10 due to a significantly greater rate of decline in BMD. These results were robust even when annual changes in weight over the study period and body composition variables were included in the regression model. There were significant gender and racial interactions with time in predicting femoral neck BMD, but these interactions did not account for the finding that obese older adults lose more BMD over time.

Study results varied by BMD site with significant BMI category differences over time found in the femoral neck site but not the total hip. Significant results in the femoral neck region could be due to the higher composition of cortical bone compared to the hip region, which has more trabecular bone(Beck, Looker, Ruff, Sievanen, & Wahner, 2000; Beck et al., 2001). Obesity is associated with higher levels of trabecular bone and lower levels of volumetric BMD due to adipose tissue (18). Another likely cause is the expansion of the bone diameter with aging, causing a larger bone with thinner walls and less bone density in the femoral neck(Beck et al., 2001).

Similar to the current study, Holecki et al.(Holecki et al., 2012) found femoral neck bone loss among obese postmenopausal women. However, these results are inconsistent with other studies that have found obesity to be protective against bone loss(Saarelainen et al., 2012). More research in this area is needed, particularly given the shifting demographics within the US aging population that is simultaneously becoming

obese at younger ages and is living longer in overweight and obese status(Leveille et al., 2005).

It remains unclear why femoral neck bone loss varies by obesity status in older adults. Obesity is associated with chronic inflammation, which is associated with the development and progression of osteoarthritis(Cao, 2011) and with bone loss. Changes in important bone-related health conditions over time that were not accounted for in study analyses (only controlled for baseline health status) may be the driving mechanism underlying the dramatic bone loss. Therefore, dramatic bone loss among obese older adults may in fact be due to post-baseline changes in levels of fat mass(Marin et al., 2010; Reid et al., 1994; Wu, Ames, Clearwater, Evans, Gamble, & Reid, 2002b), physical activity(Etherington et al., 1996; Rikkonen et al., 2010; Wilsgaard et al., 2009), bone-active medication(Taaffe, Cauley, Danielson, Nevitt, Lang, Bauer, & Harris, 2001a) and vitamin use(Jackson et al., 2006; Karkkainen et al., 2010; Moschonis et al., 2010), and the severity of diabetes(Schwartz et al., 2005). Future research will need to consider these factors as recent studies have found obesity to be associated with risk of fracture(J. E. Compston et al., 2011).

This study had a number of strengths, including the large sample size, extensive set of covariates to control for confounding, and the longitudinal study design. There are also important limitations to study findings that should be noted. The study sample draws from a healthy cohort of older adults that were disability free at baseline (age 70-79). This group of older adults is most likely different from the larger aging population and therefore study results may not be generalizable to the entire US older adult population. However, Health ABC inclusion criteria are comparable to large population based studies

such as the Longitudinal Study on Aging [LSOA](Corder L.S. & Manton K. G., 1991). The study did not examine change in BMI over time as it relates to bone loss, although sensitivity analyses examined weight change over time. Fluctuations in body weight can greatly impact bone loss(Alekel et al., 1999; Felson et al., 1993), however the majority of older adults in Health ABC maintained stable weight over time, and only experience small declines after age 70(Newman et al., 2001; Wallace & Schwartz, 2002). The study did not examine changes in potential confounding variables over the study period that could account for the significant association found among obese and femoral neck bone loss. Lastly, there may have been important differences in those individuals lost to follow-up or missing on study covariates that could have biased study results, especially if missing individuals were sicker than observed participants.

In conclusion, study findings suggest that obese older adults lose more femoral neck BMD over time compared with normal weight older adults. These results are contrary to many cross-sectional studies that have found a protective association between obesity and osteoporosis. Study findings underscore the importance of looking at the longitudinal relationship between obesity and bone loss among older adults given increasing prevalence and duration of obesity among older adults.

CHAPTER 6. ARTICLE 3: INCIDENT HIP FRACTURE BY BODY MASS INDEX CATEGORY AMONG US OLDER ADULTS[3]

6.1 ABSTRACT

Overweight and obesity are thought to be protective against hip fracture. However, recent studies have documented more hip fractures among overweight and obese older adults than underweight older adults. The objective of this study was to determine the association between overweight or obesity and hip fracture in a sample of U.S. older adults. Data from 2,790 U.S. adults ages 65 and older examined in the National Health and Nutrition Examination Survey (NHANES) III from 1991-1994 was linked to Center for Medicare and Medicaid claims data (1991-2007) to assess incident hip fractures by BMI category. The main study outcome was time to first hip fracture based on ICD-9

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codes (820.*xx*) from Medicare claims. Survival analysis was used to test whether risk of incident hip fracture differed in the overweight and obese compared to normal weight older adults, controlling for socioeconomic factors, low bone mineral density, physical activity, calcium and vitamin D intake, chronic conditions, prior hip fracture, fall frequency, self-reported health status, cognition, bone-active medications, performance measures, current smoking status, and past year alcohol use. Effect modifiers such as age, sex, and race were also examined. The majority of the baseline sample was either overweight (40%) or obese (23%). Thirteen percent experienced a hip fracture during follow-up. Cox proportional hazard models revealed that the unadjusted risk of hip fracture for overweight ($p=0.16$) and obese ($p=0.78$) were not statistically different than normal weight older adults. In adjusted models, obese older adults had a 15% lower risk of hip fracture ($HR=0.85$, $p=0.01$) compared to normal weight older adults, controlling for a range of covariates. Risk of hip fracture was not significantly different for overweight and normal weight older adults ($p=0.21$). The relationship between BMI category and hip fracture did not differ by age, gender, or race (non-significant interaction terms). Study results confirm the protective effect of obesity on risk of hip fracture in a nationally representative sample of US older adults. Surprisingly, overweight adults were at a similar risk as normal weight adults. Future research should continue to understand the complex relationship between body mass, bone mass, and risk of fracture, particularly among a dramatically changing demographic of older adults.

6.2 INTRODUCTION

Osteoporosis-related fractures currently affect 2 million older adults, and this number is expected to increase to 3 million by 2025(Burge et al., 2007). Costs related to fractures are also expected to increase(Burge et al., 2007). Hip fractures, the most devastating type of osteoporotic fracture, are associated with increased risk of disability and mortality(Magaziner et al., 2003).

The majority of prior literature finds that overweight and obesity are protective against risk of hip fracture(Beck et al., 2009; De Laet et al., 2005; DiPietro et al., 1993; Wolinsky et al., 2009). However, many studies have assessed fracture via self-report instead of more accurate, site specific measures such as medical records(Chen et al., 2004). Most studies have focused on postmenopausal, white women and not used samples that are generalizable to the US older adult population, excluding men and racial and ethnic minorities. Although hip fracture incidence is lower in these populations (Orwig, Chan, & Magaziner, 2006), there may be important differences in the association between body mass categories and hip fracture by gender and race(Wolinsky et al., 2009). Previous research has not examined this association with adequate control for confounding variables such as bone mineral density and functional and health status.

Recent findings illustrate a number of inconsistencies in the literature related to and body mass index (BMI) and risk of hip fracture. The association between BMI and hip fracture may be nonlinear(De Laet et al., 2005). Risk of hip fracture is highest among older adults with low BMI, but this does not necessarily translate to increasing protection as BMI increases(De Laet et al., 2005; Premaor et al., 2010; Premaor et al., 2011). More importantly, overweight and obese individuals account for about half of all hip fractures

compared to underweight older adults who account for 4% of hip fractures(Nielson et al., 2012).

Therefore the objective of this study was to examine the association between body mass categories and risk of incident hip fracture in a nationally representative U.S. sample utilizing linked Center for Medicare and Medicaid Services claims providing 16 years of follow-up. The large, generalizable sample size of this study design provides the ability to examine potential effect modifiers such as age, gender, and race. Additionally, the rich baseline dataset allows for the adequate control of risk factors related to both body mass and hip fracture such as health status and physical function.

6.3 METHODS

Baseline data was obtained from the third National Health and Nutrition Examination Survey (NHANES III, 1988-1994) which includes health and nutritional status information from a nationally representative sample of the non-institutionalized U.S. population. Follow-up data were obtained by linking NHANES III data to Medicare enrollment and claims records and NHANES III Linked Mortality File (restricted data obtained from the National Center for Health Statistics' Research Data Center). Medicare claims data were available for 1991-2007, providing over 16 years of follow-up to observe time to incident hip fracture claims.

The study sample included 4,874 individuals ages 65 and older at baseline (during their NHANES III interview) linked to CMS claims. Individuals who were enrolled in Medicare-managed care plans (identified through the Medicare Denominator file) at baseline (N=208) or for the entire follow-up period (N=28) were excluded. Individuals

who had a claims-based hip fracture before (N=14) or at baseline were also excluded (N=13). The sample was further restricted to those not missing on BMI (N=676) or BMD (N=728), not underweight (n=117), and not missing on study covariates (N=300) leaving a final sample of N=2,790.

BMI categories were based on measured weight and height (in kilograms divided by meters squared). BMI was categorized as normal (BMI: 18.50-24.99), overweight (BMI: 25.00-29.99) and obese (BMI: > 30.00). The sample excluded underweight individuals (BMI<18.50) as the relationship between underweight and hip fracture has been widely studied(Ravn et al., 1999). Additionally, the underweight BMI group represents a small proportion of the total BMI range (around 2%).

OUTCOME

Incident hip fracture cases were identified using Medicare claims from 1991-2007 among NHANES III participants who were successfully matched to Medicare claims data. Hip fracture cases were primarily identified (99%) based on an inpatient diagnosis of ICD-9-CM code 820 unless there was a concurrent code indicating a previous hip fracture or other bone disease (codes 905.4, 966.4, 996.6, 996.7, E878.1, 733.4, 773.8, 733.9, 198.5, V540, V664, V674)(Looker & Mussolino, 2008). Additional methods, including the use of mortality data indicating that death was associated with a hip fracture, were used to identify additional hip fracture cases(Looker & Mussolino, 2008; Ray, Griffin, Fought, & Adams, 1992). A time to event indicator variable was created to identify individuals with a hip fracture during the follow-up period (individuals who died were right censored).

BASELINE CHARACTERISTICS

Socioeconomic factors were self-reported and included poverty income ratio (a ratio of family income to poverty threshold, 0-5, missing values were imputed based on the sample mean), education (<9th grade, 9-11 grade, 12th grade completed, some college completed, college graduate), and marital status (married versus widowed/ divorced/ separated/ single).

Common risk factors for hip fracture were examined, including low BMD, physical activity, health status, cognitive function, bone-related vitamin and medication use, current smoking status, and average alcohol use in the past year. Low BMD (g/cm^2), measured via dual energy x-ray absorptiometry (DXA) at the femoral neck, was defined by a dichotomous variable (<0.79 g/cm^2 for men and <0.74 g/cm^2 for women, which corresponds to a T-score below -1)(Looker, Orwoll, Johnston, Lindsay, Wahner, Dunn, Calvo, Harris, & Heyse, 1997b). Physical activity (continuous summary measure) was assessed by self-report of 10 physical activities engaged in within the previous month (walking, jogging, bike riding, swimming, aerobics, dancing, calisthenics, gardening, lifting weights, and other activities) and the intensity level of each activity was based on recommended cut points of metabolic equivalent (MET) scores(Ainsworth et al., 1993). Health status included fall frequency within past year and prior hip fracture (dichotomous variables based on self-report), any activities of daily living (ADL) limitations (any difficulty dressing, getting in and out of bed, and eating), excellent-good self-reported general health status (dichotomous variable), chronic conditions (dichotomous variables for diabetes, hypertension, cardiovascular disease, stroke, thyroid disease, and cancer). A short index of cognitive function (continuous variable) was based on seventeen questions

about orientation, recall, and attention. Bone-related vitamin and medication use included self-reported use (yes/no) of calcium supplements, vitamin D supplements, osteoporosis medications, and steroids. A dichotomous variable was created for current smoking status (some everyday or some days versus not at all). A continuous measure was used for average alcohol use (days) within the past year.

STATISTICAL ANALYSIS

Tests of significance were used to determine if study covariates differed by hip fracture (Table 6-1). F tests were used from generalized linear regression models for continuous covariates and chi-square tests of significance were used for categorical/ dichotomous covariates. Cox proportional hazard ratios were used to examine if time to first event differs for overweight and obesity with normal as the reference (Model 1, Table 6-2). Model 2 controlled for the following confounders: income, education, marital status, low BMD, physical activity, calcium intake, vitamin D intake, prior hip fracture, fall frequency, activities of daily living limitations, health status, chronic conditions, prescription medications (steroids and bisphosphonates), cognitive function, smoking status and alcohol use. Models 3-5 examined age, sex, and race to determine if these variables were effect modifiers between BMI categories (overweight and obese) and hip fracture. To account for the complex survey design and to make results representative of the US population, all analyses used NHANES III sampling design parameters.

6.4 RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

The prevalence of baseline overweight and obesity in this sample was 40% and 23%, respectively. The sample had a mean age of 72.89 (SD=6.06), was 89% white, and 56% female. Table 6-1 displays characteristics of the study sample by hip fracture status. Thirteen percent of the sample self-reported at least one hip fracture during the follow-up period. The mean BMI was lower among individuals that experienced a hip fracture ($p<0.001$). Individuals who experienced a hip fracture were more likely to be older, female, white, and have ADL limitations ($p<0.01$). Individuals experiencing a hip fracture were less likely to be married, had lower levels of calcium intake, and had a lower mean BMD of the femoral neck ($p<0.05$).

Table 6-1. Sample Characteristics at Baseline by Hip Fracture Status, NHANES III, n=2,790

	Hip Fracture	**No Hip Fracture**	**P-value**
Weighted %	13.0	87.0	
Body mass index (kg/m^2), mean (SD)	25.8 (4.1)	27.0 (4.6)	<0.001
Normal [BMI 18.5-24.99] (%)	51.5	34.2	
Overweight [BMI 25-29.99] (%)	32.6	41.5	
Obese [BMI ≥ 30] (%)	15.9	24.3	
Age in years, mean (SD)	74.5 (6.0)	72.7 (6.0)	<0.001
Female (%)	73.2	53.1	<0.001
Race (%)			0.003
White	94.8	87.6	
Black	3.4	7.4	
Mexican American	1.2	1.9	
Other Race	0.7	3.1	
Poverty income ratio, mean (SD)	2.8 (1.8)	3.0 (1.9)	0.093
Married (%)	53.24	61.4	0.043
Education , mean (SD)	10.9 (3.1)	11.2 (3.6)	0.402
Physical activity (metabolic equivalent score), mean (SD)	7.2 (6.1)	7.9 (6.6)	0.110
Calcium intake (mg) , mean (SD)	718.6 (401.5)	814.7 (494.9)	<0.001
Vitamin D (mcg), mean (SD)	11.9 (75.8)	8.3 (21.0)	0.461
BMD of femoral neck (g/cm^2), mean (SD)	0.611 (0.112)	0.708 (0.142)	<0.001
Low BMD (%)	91.2	68.2	
Fall frequency (%)	25.8	20.6	0.128
Prior hip fracture (%)	4.2	2.4	0.078
Any ADL limitations (%)	21.3	13.3	0.005
Excellent-good health (%)	76.7	73.2	0.174
Diabetes (%)	10.4	12.4	0.415
Hypertension (%)	46.9	46.6	0.945
Cardiovascular disease (%)	17.2	19.5	0.448
Stroke (%)	5.6	7.2	0.532
Thyroid disease (%)	10.6	7.2	0.119
Cancer (%)	11.4	9.6	0.329
Short index of cognitive function, mean (SD)	13.3 (2.9)	13.7 (2.9)	0.078
Osteoporosis medications (%)	5.4	4.7	0.653
Steroid medications (%)	2.9	2.2	0.526
Current smoker (%)	11.8	11.1	0.805
Alcohol in past year, mean (SD)	45.6 (99.0)	58.7 (114.6)	0.059
Died	8.6	4.4	0.154

BODY MASS INDEX CATEGORIES AND RISK OF HIP FRACTURE

Table 6-2 displays hazard ratios for hip fracture by BMI category. Risk of hip fracture by BMI category was not significantly different in unadjusted results. Controlling for a range of covariates (Model 2), obese older adults had a 15% lower risk of hip fracture (HR=0.85) compared to normal weight older adults ($p<0.01$). However, overweight older adults' risk of hip fracture was not significantly different from normal weight older adults in the adjusted model ($p=0.21$). Age ($p=0.50$), gender ($p=0.20$), and race ($p=0.62$) were not significant effect modifiers of the relationship between BMI categories and risk of hip fracture.

Table 6-2. Hazard Ratios (HR) of Hip Fracture by Body Mass Index Categories, =2,790†

	Model 1		Model 2		Model 3		Model 4		Model 5	
	HR	p value	HR	p value	HR	p value	HR	p value	HR	p value
Obese	0.93	0.16	0.85	0.01	0.83	0.02	0.79	0.01	0.82	0.06
Overweight	0.99	0.78	0.94	0.21	0.97	0.62	0.87	0.08	0.93	0.41
Age ≥73	--	--	--	--	1.64	0.00	--	--	--	--
Obese * Age ≥73	--	--	--	--	1.08	0.58	--	--	--	--
Overweight * Age ≥73	--	--	--	--	0.93	0.46	--	--	--	--
Female	--	--	--	--	--	--	0.61	0.00	--	--
Obese * Female	--	--	--	--	--	--	1.14	0.23	--	--
Overweight * Female	--	--	--	--	--	--	1.15	0.16	--	--
White	--	--	--	--	--	--	--	--	1.04	0.68
Obese * White	--	--	--	--	--	--	--	--	1.13	0.31
Overweight * White	--	--	--	--			--	--	1.01	0.90

†Models 2-6 controlling for low bone mineral density, physical activity, calcium intake, vitamin D intake, age, sex, race, education, income, prior hip fracture, fall frequency, activities of daily living limitations, health status, chronic conditions, prescription medications, cognitive function, smoking status and alcohol use. P-values for F test from interaction terms for Model 3: bmi*age ≥73 (p=0.498), Model 4: bmi*female (p=0.198), and Model 5: bmi*white (p=0.552).

6.5 COMMENT

Obesity was found to be protective against risk of hip fracture in a nationally representative sample of US older adults. Overweight and normal weight older adults had a similar risk of hip fracture. Risk of hip fracture did not vary by age, gender, or race.

COMPARISON WITH EXISTING STUDIES

Prior studies have largely found obesity to be protective against hip fracture. De Laet (2005) found a one unit increase in BMI was associated with a 3% reduced risk (RR=0.97) of hip fracture in a large, international sample. Similar results have been found in US samples. Morbid obesity was associated with a 70% lower rate of hip fracture in an NHANES I sample(Premaor et al., 2010). Incidence of hip fractures was found to decline with increasing BMI among older women in a more recent US sample(Beck et al., 2009). The most similar study to the current was by Wolinsky et al. (2009) which found an unadjusted and adjusted, protective effect of overweight and obesity against hip fracture. Important differences between study samples may explain the different findings. For example, the Wolinsky study had a lower prevalence of overweight (36%) and obesity (14%) and included underweight older adults (4%) whereas the current study excluded the underweight BMI category from the sample and had a larger prevalence of overweight (40%) and obese (23%) older adults.

Prior research has found obesity to be detrimental to risk of fracture, but only for sites other than the hip. Compston (2010)(J. E. Compston et al., 2011) found that obesity increased the risk of incident ankle and upper leg fractures among older women, but found that obese were at a lower risk for wrist, hip, rib, and pelvis fractures. Nielson

(2010)(Nielson et al., 2010) found an increased risk of non-spine fracture among obese older men; however, this result was accounted for by mobility limitations. These results indicate poor bone quality among heavier individuals. Studies have found that obese women, when accounting for body size, have less relative bone strength than their normal weight counterparts(Beck et al., 2009). With future cohorts of older adults having spent more of their lives obese(Leveille et al., 2005), future research will have to investigate the long term effects of excessive fat mass on bone quality.

STUDY LIMITATIONS

There are a number of limitations to the study that should be mentioned. The most notable is a lack of follow-up measures for the independent variable and study covariates. Without measures of BMI at follow-up, we are unable to determine if individual changed BMI categories prior to hip fracture. Change in weight has been shown to be associated with risk of fracture with increasing weight protecting against fracture and declines in weight increasing fracture risk(Felson et al., 1993; Rosen & Bouxsein, 2006). Additionally, other important confounding variables may have changed during the follow-up period and we are unable to account for these changes. Study results may be limited due to measurement error related to the independent variable. BMI is not an ideal measure of fat mass and therefore may not be appropriate to operationalize obesity. If hip fractures are prevalent among overweight and obese older adults, then there are important factors about higher body mass that may not be accurately captured by BMI. Other measures of body composition such as waist circumference and total fat mass are better

measures of fat mass and may more accurately reflect the negative aspects of higher body mass categories. Lastly, even though the NHANES sample makes results of this analysis representative to the US older adult population, the sample is comprised of individuals who took part in the examination part of the interview who may be different than individuals who were only interviewed.

STUDY ADVANTAGES

The current study has a number of important strengths. This study had a number of strengths, including the nationally representative, large sample size that provides population-based estimates and allows for examination of potential effect modification. The linkage of NHANES to Medicare data provided the ability to accurately assess the occurrence of a hip fracture via ICD-9 codes and to observe a rare event in the 16 years of follow-up. Lastly, NHANES includes a rich set of measures to examine body composition and bone mass, as well as an extensive set of covariates.

6.6 CONCLUSIONS

Study results confirm the protective effect of obesity on risk of hip fracture in a nationally representative sample of US older adults. Obese older adults had a 15% lower risk of hip fracture compared to normal weight older adults. However, overweight older adults had a similar risk of hip fracture as normal weight older adults. The relationship between BMI categories and risk of hip fracture did not vary by age, gender, or race.

These results should be considered in light of an emerging literature showing these groups should not be ignored related to falls and fracture screening. This is

especially true considering that the prevalence of overweight and obesity continues to increase among cohorts of older adults. Therefore, using only low BMI as a clinical indicator of risk of fracture may not be useful among future cohorts of older adults. Future research should continue to understand the complex relationship between body mass, bone mass, and risk of fracture, particularly among a dramatically changing demographic of older adults.

CHAPTER 7. DISCUSSION

7.1 SUMMARY

There are a number of reasons why obesity is thought to protect against bone loss and risk of fracture. First, overweight and obese individuals their bones to more load, which has been shown to increase bone mass (Felson et al., 1993; Glauber et al., 1995; Ribot et al., 1994; Rosen & Bouxsein, 2006). Second, adipose tissue is associated with higher levels of estrogen and higher levels of estrogen have been shown to protect against bone loss(Felson et al., 1993). Additionally, higher levels of body fat have been shown to reduce the rate of bone resorption(Rosen & Bouxsein, 2006). Lastly, excess fat may protect an individual during a fall by providing extra padding and potentially prevent a fracture from occurring(Beck et al., 2009).

However, there is a growing literature indicating that even with the protection of higher BMD, some obese older adults experience falls and fracture. Extremely obese postmenopausal women are more likely to report falling and experiencing a fracture(Beck et al., 2009). Risk of falls may be increased in obese older adults as they may have poor balance, muscle strength, and mobility issues(Gnudi et al., 2009; Premaor et al., 2010). Even though more padding from heavier BMI may be seen as potentially protective against injury, this protection could be offset by the heavier weight itself causing a higher impact in the event of a fall(Beck et al., 2009; Premaor et al., 2010). Additionally, studies have shown that soft tissue padding is insufficient to prevent a fracture (Bouxsein et al., 2007; Nielson et al., 2009; Robinovitch, McMahon, & Hayes, 1995).

To date, literature on the cross-sectional association between obesity and osteoporosis has been mixed with some studies finding a protective effect(Albala et al., 1996; Asomaning et al., 2006) while others found obesity has a negative association with osteoporosis(Greco et al., 2010; Lin et al., 2010). Results from Paper 1 of this dissertation confirmed a positive cross-sectional association between BMI and BMD in a nationally representative sample of US older adults. Figure 4.1 illustrates the positive association between these two variables showing that BMD increases as BMI increases. Even though there are important differences in bone and fat mass by age(Kyle et al., 2001; Lips, 1997b), race(Kessenich, 2000a; Peacock, Buckwalter, Persohn, Hangartner, Econs, & Hui, 2009a), and gender(Albrand, Munoz, Sornay-Rendu, DuBoeuf, & Delmas, 2003b; Blaak, 2001), this study did not find significant demographic differences in the BMI and BMD association. This may provide more evidence for the limitations of using BMI as a measure of adiposity, particularly among older adults(Ribot et al., 1994). Although BMI is a quick, easy measure of body composition that is widely used, especially in relation to assessing risk of osteoporosis(Kanis et al., 2005), it may have limitations in its usefulness in predicting bone-related outcomes(Robbins, Schott, Azari, & Kronmal, 2006). Studies that have used other measures of body composition reveal that higher levels of fat mass, regardless of the BMI level, have deleterious effects on bone(Hsu et al., 2006; Zhao et al., 2007).

Although cross-sectional data show a positive association between BMI and BMD, results from Paper 2 of this dissertation using longitudinal data show that obese older adults lose more bone density over time compared to normal weight older adults. Figure 5.2 displays the longitudinal relationship between baseline BMI and change in

femoral neck BMD. Sensitivity analyses showed that these results did not change after accounting for demographic interactions or by weight change over the study period. Similar to cross-sectional findings, obese older adults began with the highest BMD at baseline compared to overweight and normal weight older adults. However, by year 10, obese older adults have the lowest BMD compared to other BMI categories. It remains unclear why there is varying bone loss by BMI category and what mechanisms are driving the dramatic bone loss among obese older adults.

The finding that obesity is associated with bone loss over time among older adults may help explain why more hip fractures occur in higher BMI groups. For example, a higher percentage of hip fractures occur among overweight and obese older adults (47%) compared to underweight older adults (4%), those considered to be at most risk of hip fracture.(Nielson et al., 2012) Many studies show that risk of hip fracture declines as BMI increases(De Laet et al., 2005; Wolinsky et al., 2009). However, the literature on the association between obesity and risk of hip fracture has also been inconsistent(J. E. Compston et al., 2011). Paper 3 investigated the risk of hip fracture in a nationally representative sample of US older adults over a 16 year period. Results confirmed the independent, protective effect of obesity on risk of hip fracture. Obese older adults had a 15% lower risk of hip fracture compared to normal weight older adults. Surprisingly, this study found that overweight older adults had a similar risk of hip fracture as normal weight older adults. The relationship between BMI categories and risk of hip fracture did not vary by demographic factors such as age, gender, or race. Additionally, this relationship was not found to vary by low BMD.

Results from this dissertation confirmed the protective association between higher BMI and osteoporosis in Paper 1. However, results from Paper 2 found the relationship between obesity and osteoporosis changes over time. Even though obese older adults had higher BMD at baseline, this group lost more bone mass over the 10-year study period. Results from Paper 1 and 2 provide useful information about the relationship between obesity and bone-related outcomes like osteoporosis and bone loss as measured by BMD. These outcomes are most clinically useful in relation to predicting risk of fracture. However, results from Paper 3 are in contrast to results from Paper 2 in that obese older adults were found to lose more femoral neck BMD over time but were not at risk for hip fracture. It is possible that BMD is not an appropriate marker for hip fracture risk among obese older adults and that other measures of bone quality and strength may be more indicative of fracture risk. Additionally, prior research has found obese older adults to have an increased risk of ankle and leg fractures whereas other factors associated with obesity may protect from fracturing their hip (extra padding around the hip and limited exposure to falls due to limited physical activity). Where study results across Papers 2 and 3 were consistent is in the similar risk of bone loss and hip fracture among the overweight and normal weight groups. This is in contrast to prior studies that have found overweight groups to have a similar protection against bone loss and fracture as obese older adults.

7.2 PUBLIC HEALTH RELEVANCE

Research on the intersection of overweight/obesity and osteoporosis/hip fracture is of significant public health concern as older adults will represent 20% of the US

population by 2030(Knickman & Snell, 2002); the majority of whom will be overweight or obese(Flegal et al., 2010) and/or will have low bone mineral density(Looker, Borrud, Dawson-Hughes, Shepherd, & Wright, 2012). Current interventions related to osteoporosis and hip fracture prevention do not target overweight or obese older adults(Davisson et al., 2009; Nayak, Roberts, & Greenspan, 2009). Based on these findings, this could translate into a large segment of the older population being undiagnosed for osteoporosis and missed for hip fracture prevention. Current strategies to prevent and treat bone-related diseases and health events may not be appropriate for overweight and obese older adults, particularly if the mechanisms them differ for this segment of the population(Premaor et al., 2010; Premaor et al., 2011). Furthermore, the relationship between obesity and osteoporosis may be changing as successive cohorts of older adults have spent a larger proportion of their lives obese(Leveille et al., 2005). Early exposure to high levels of fat mass may have deleterious impacts on the development of peak bone mineral density(Felson et al., 1993; Ribot et al., 1994) which could drastically increase the risk of osteoporosis and hip fracture in later years. Early onset of obesity could result in early development of diabetes, which dramatically increases an individual's risk for falls, bone loss, and hip fracture(Schwartz et al., 2005). Outcomes related to obesity and osteoporosis represent significant public health issues among older adults that are costly to the health care system(Braithwaite et al., 2003). The added burden placed on resources and spending is likely to dramatically increase in the near future(Burge et al., 2007; Rice & Fineman, 2004).

7.3 FUTURE DIRECTIONS

This research sought to address the conflicting findings currently present in the literature on obesity and bone-related outcomes. More research is needed on the obesity and osteoporosis/hip fracture paradox that is critical to bringing attention to clinical care provided to a large segment of at-risk older adults. Particularly when physicians and older adults do not perceive the bone-related health risks associated with higher BMI categories(Nayak et al., 2009).

Results from this dissertation found that obesity and osteoporosis were positively associated in cross-sectional data. Future research could use other measures of body compositions, such as fat mass, to operationalize obesity more appropriately among older adults as many studies have shown BMI to have limitations in this population(Ribot et al., 1994; Zhao et al., 2007). Additionally, other measures of osteoporosis such as volumetric bone mineral density could be used to further explore the complex relationship between body mass and bone-related outcomes among heavier older adults as this measure would account for the added mass of an obese older adult and would not inflate the BMD value as is often the case with using BMD measured via DXA(Sukumar et al., 2011). This is particularly relevant as BMD may not be an adequate measure of fracture risk among obese older adults. Bone quality and strength may be more useful in predicting risk of fracture than BMD alone. For example, when accounting for body size, obese women have less relative bone strength than their normal weight counterparts (Beck et al., 2009). Instruments such as quantitative computer tomography (QCT) provide measurement of bone strength and quality, but are not useful techniques in the

clinical setting(Hans et al., 1997). Better measures of bone strength (beyond DXA) and quality are needed, especially in the context of obesity.

Future research should examine the mechanisms driving the larger bone loss among obese older adults found in Paper 2. Chronic inflammation and changes in factors such as body composition, disease severity, nutrition, disability and functional status, as well as medication use could explain the higher bone loss among obese older adults.

Lastly, it is possible that obese older adults with a hip fracture may have worse outcomes compared to other older adults with a hip fracture. Obese older adults already have higher levels of disability and chronic conditions(Alley & Chang, 2007; Bales & Buhr, 2008), both of which are associated with worse outcomes post hip-fracture(Himes & Reynolds, 2011; Maggi et al., 2010). This may even result in higher risk of disability and mortality post-hip fracture among obese older adults.

7.4 LIMITATIONS AND STRENGTHS

LIMITATIONS:

Measurement issues related to osteoporosis may play a role in the inconsistent findings related to the protective effects of extra weight on BMD. Obtaining accurate measurements of BMD via DXA machines in obese individuals can be difficult and can result in elevated BMD measurements(Uppot, Sahani, Hahn, Gervais, & Mueller, 2007). Fat deposits and correct positioning are common issues with DXA measurement among larger individuals (Kanis, 2002a; Rosen & Bouxsein, 2006). Inflated BMD measurements due to measurement error could downwardly bias the prevalence of osteoporosis and low BMD among obese older adults. Another potential measurement limitation is that

overweight and obese individuals may not be able to obtain a DXA scan and are systematically more likely to be missing on the BMD measurement (Paper 1). For example, NHANES excludes individuals who weigh over 300 pounds(National Center for Health Statistics, 2007a) from DXA measurements due to limitations of the scanning area on DXA machines (Tataranni & Ravussin, 1995).

Results from these papers were limited to measurement of osteoporosis and bone loss via BMD and were not able to explore other measures of bone quality and strength. Using BMI and BMD across the three papers provided consistently in measurement but limited the scope of research. These results are also limited in the type of fractures examined in Paper 3, which focused on the most clinically relevant type of fracture as opposed to looking at a more comprehensive range of fractures. This makes results from Paper 3 limited in discussing risk of fracture, particularly as prior research has shown obese to be at a higher risk of other types of fractures.

In regards to measurement for obesity, BMI is a commonly used measure in many large, epidemiologic studies and in clinical settings. However, older adults who have lost height due to vertebral compression fractures may have elevated BMI values. If accurate height is not reported, the association of BMI and BMD may be confounded (Looker et al., 2007). Additionally, BMI is not a great measure of fat mass and is unable to distinguish between the composition and distribution of body mass, both of which have important implications for bone-related outcomes. Other measures of body composition such as waist circumference and total fat mass are better measures of fat mass. However, only single slice abdominal CT scans can distinguish between visceral and subcutaneous

fat, both of which having differing effects on bone outcomes.(Jensen, Kanaley, Reed, & Sheedy, 1995)

STRENGTHS

Results from this dissertation provide a comprehensive examination of the association between obesity and bone-related outcomes using diverse sample of older adults. The main strength of this study was its ability to comprehensively explore the association between higher BMI and bone-related outcomes utilizing multiple datasets and methods. This study was able to summarize findings on multiple outcomes and discuss study implications in relation to one another. For example, higher BMI provides obese older adults with higher BMD at baseline, but regardless of this, this weight group lost more bone mass over time and may therefore be susceptible to fracture.

Throughout these papers, the same predictor and many of the same covariates were used to ensure consistency across results. Datasets selected for these studies contained the preferred measurement of variables including BMD from DXA scans as well as hip fracture events from claims data. In studying hip fracture incidence, the use of claims data is preferred over self-reported hip fracture events which are prone to measurement error. All study datasets had measured height and weight to create a more accurate BMI measure compared to self-reported BMI which is also prone to measurement bias. The datasets used in each paper offered a rich set of variables to control for factors related to the predictor and outcome. The NHANES datasets and Health ABC data offered a range of high quality health-related measures including

physical activity, functional status, bone-related medication and vitamin use, as well as weight change.

Large sample sizes from each of the datasets selected for this study provided adequate power to detect meaningful differences in study outcomes. Additionally, large sample sizes facilitated the examination of demographic interactions that were tested in each article. The use of NHANES data in Paper 1and 3 provided samples that were generalizable to the national population of older adults. Datasets selected for Paper 2 and Paper 3 provided longitudinal data, which allowed for the establishment of temporal relationships between the independent and dependent variables.

7.5 CONCLUSIONS

It had long been assumed that the mechanical loading of extra weight prevented osteoporosis and risk of hip fracture. However, the relationship between body mass and bone health may be more complex. Many cross-sectional studies, including results from Paper 1 of this dissertation, have shown obese older adults have higher BMD compared to normal weight older adults. However, results from Paper 2 of this dissertation using longitudinal data show that obese older adults lose more bone density over time. The mechanisms associated with the larger bone loss among obese older adults remain unknown, but may explain why almost half of all hip fractures occur among heavier older adults. Prior literature on the protective effect of obesity on risk of fracture is mixed, although the majorities of studies, as well as Paper 3 of this dissertation, have found obesity to be protective against hip fracture risk. Most surprisingly, Paper 3 found that overweight older adults had the same risk as those of normal weight. Current

interventions related to osteoporosis and hip fracture prevention do not target overweight or obese older adults. Based on these findings, this could translate into a large segment of the older population being undiagnosed for osteoporosis and missed for hip fracture prevention.

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