THE ASSOCIATION BETWEEN RHEUMATOID ARTHRITIS, BONE STRENGTH, AND BODY COMPOSITION WITHIN THE WOMEN'S HEALTH INITIATIVE

By

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A Dissertation Submitted to the Faculty of the
MEL AND ENID ZUCKERMAN COLLEGE OF PUBLIC HEALTH

In Partial Fulfillment of the Requirements
For the Degree of

DOCTOR OF PHILOSOPHY
WITH A MAJOR IN EPIDEMIOLOGY

In the Graduate College

THE UNIVERSITY OF ARIZONA

2010

THE UNIVERSITY OF ARIZONA
GRADUATE COLLEGE

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ACKNOWLEDGEMENTS

I would like to acknowledge the participants of the Women's Health Initiative (WHI), without whom this dissertation and other important women's health studies could not be performed. The WHI program is funded by the National Heart, Lung, and Blood Institute through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221.

I would also like to thank the National Institute of Arthritis and Musculoskeletal and Skin Disease for funding the hip geometry analysis through R01 AR049411, and providing dissertation support through R01 AR049411-04S1.

I would like to thank my dissertation committee, Dr. Zhao Chen, Dr. Jeffrey Lisse, Dr. Duane Sherrill, and Dr. Jane Mohler, for all of their help and mentoring through this dissertation process. I would also like to thank Dr. Sydney Pettygrove and Dr. Paul Hsu for serving on my comprehensive exam committee and for all of their help in the formation of this dissertation.

I would like to thank the following investigators for their guidance as coauthors on my dissertation papers: Dr. Thomas J. Beck, Dr. Tamsen Bassford, Dr. Jane Cauley, Dr. Andrea LaCroix, Dr. Beth Lewis, Dr. Scott Going, Dr. Charles Eaton, and Dr. Brian Walitt. I would also like to thank Mary Carney, LeaEllen Ren, and the members of the WHI Publications and Presentations committee for all of their assistance and review during this process.

I would like to thank Leslie Arendell, Skye Nicholas, and Guanglin Wu for being fantastic colleagues at the Healthy Aging Lab. Thank you for being great sounding boards for any and all questions or problems during our time together.

I would like to thank the past and previous members of the Office of Student Services and Alumni Affairs, especially Chris Tisch and Linda Dobbyn for their continual support and friendship over the years. I would also like to thank the Epidemiology and Biostatistics faculty, especially Elizabeth Jacobs, Robin Harris, and Denise Roe.

I would like to thank Kristen Pogreba-Brown, Ryan Brown, Jennifer Kozik, and Jerry Poplin, for seven years of friendship. In addition to their endless support during the masters and doctoral programs, I would not have survived many things (a lumbar puncture and a windy bike ride come to mind) without their motivation and inspiration. I know that BF Epi and its subsidiary companies will be successful business ventures, but I am even more positive that I have been blessed with bona fide friendships that I know will continue in the future.

I would also like to thank Samantha Goodwin, Billie Winegard, Anneke Jansen, and Adrianna Cimetta for their friendship. I will forever value the love and support you have given me. Many thanks go to Sarah Steudler, Erin Snell, Jeanette Olli, Lauren Melfa, John Pickett, and Nathan Painter for making my college experience so special. I would not be the person I am today without Elon and the lessons learned from each of you, and I thank you for everything from the bottom of my heart.

There are not enough words to thank Liza delos Santos for everything she has given and done for me over the years. Thank you for listening to me and supporting me through everything degree and non degree-related even if it made you TUIYM a bit.

And finally, I would like to thank my family, especially Helen and Billy Wright for being the best parents, and allowing me to pursue my dreams, even if it meant being in school for 24 consecutive years. Thank you for the spiritual and financial guidance you have given me and loving me unconditionally.

TABLE OF CONTENTS

TABLE OF CONTENTS – CONTINUED

LIST OF FIGURES

LIST OF TABLES

LIST OF TABLES – CONTINUED

ABSTRACT

Introduction: Osteoporotic fractures, a major public health problem in aging populations, can lead to increased disability and mortality. Though rheumatoid arthritis (RA) patients have a higher risk for fractures than healthy populations, it is not known how hip structural geometry and body composition, two factors associated with bone strength, affect fracture risk in this population. The **overall goal** of this dissertation is to examine the association between RA, fracture, hip structural geometry, and body composition, in the participants of the Women's Health Initiative (WHI).

Methods: The association between probable RA and fracture risk was tested using the entire WHI cohort (n=161,808). The association between probable RA and hip structural geometry was tested, both cross-sectionally and longitudinally, in a smaller sample (n=11,020) of participants from the WHI Bone Density Centers (WHI-BMD). The last study, testing the association between probable RA and body composition was also conducted in the WHI-BMD cohort.

Results: In comparison to the non-arthritic group, the probable RA group had a significant 50%, 2-fold, and 3-fold increase in any, spine, and hip fracture, respectively. The association was not mot modified by age or ethnicity, but glucocorticoid use altered the association between RA and spine fractures. In terms of geometry, the probable RA had a significantly lower ($p<0.05$) mean hip BMD, outer diameter, cross-sectional area, and section modulus at the narrow neck region compared to control groups, indicating reduced bone strength. Body composition changes were present between the probable RA and the control group, with the probable RA group having statistically lower estimate of

lean mass and statistically higher estimates of fat mass compared to the non-arthritic control group cross-sectionally and over the study.

Conclusion: These studies confirm the increased risk for fracture among RA patients, while providing evidence that RA alters bone strength, especially at the hip, and negatively effects body composition by reducing lean mass and increasing fat mass. Additional research is needed link structural geometry and body composition to bone strength to lead to tailored interventions to minimize decreases in bone strength in this high fracture risk population.

CHAPTER 1: INTRODUCTION

Osteoporosis is a major public health problem in aging populations. As a condition of generalized skeletal fragility, osteoporosis is characterized by decreases in bone strength and increases in fracture risk. Fractures associated with osteoporosis, have been shown to lead to increased pain, disability; decreased quality of life (1); and higher mortality rates (2). The costs associated with osteoporosis-related fractures are enormous, for example, it was estimated that 17 billion dollars were spent in the United States during 2005 (3). Age and bone mineral density (BMD) are the primary risk factors associated with osteoporosis and fragility fractures, but other risk factors have been identified in the literature including: gender, weight, height, history of fractures, history of parental hip fracture, smoking, alcohol use, femoral neck BMD, history of secondary osteoporosis, glucocorticoid use, and rheumatoid arthritis (RA) (1).

RA is a multi-system inflammatory disorder characterized by chronic destructive synovitis, associated with substantial adverse health consequences (4). RA affects only one percent of the adult population, however, those who are affected experience increased risk for fractures, increased risk for disability, and a reduction in average life span from 3 to 18 years (5). The limitations imposed by RA disability are associated with psychosocial problems and loss of patient and/or caregiver's income (6, 7). These outcomes have a substantial economic impact not only on the individual, but society as well (8). Direct and indirect costs for individuals with RA vary over the course of the disease, and studies have found that increases occur not only in costs directly related to RA over time, but also in those related to co-morbidities, including osteoporosis (9).

Bone strength, the key component of fracture risk, is comprise of material and structural properties of the bone. Studies have shown that low BMD is strongly correlated with increased fracture (10); however BMD is not a direct measure of either the material or structural properties of bone. The literature clearly demonstrates that RA patients have lower BMD (11-13) and increased fracture risk compared to non-arthritic controls (14-16), but there have not been any studies examining the structural consequences of bone strength in RA patients.

Recently, osteoporosis research has given more interest to the role body composition and the neural system plays in bone health, as it is well known that muscle mass and strength are important contributors to bone quality (17). In terms of body composition, RA patients experience cachexia, or muscle wasting, which compromises muscle strength and functional capacity, and is a significant contributor to reduced life expectancy (5, 18). Unfortunately, studies on the longitudinal effects of RA on body composition, and how these changes are related to bone health have been limited by size and technique.

SPECIFIC AIMS

Because RA is more common in women, and osteoporosis becomes a major concern for women after menopause, the Women's Health Initiative (WHI), a nationwide, multi-ethnic cohort of postmenopausal women, provides the perfect opportunity to study the effects of RA on osteoporosis-related fractures and variables related to fracture risk including hip structural geometry and body composition. The **goal**

of this dissertation is to assess the effect of RA on fracture, the most serious osteoporosis outcome, and two determinants of bone strength, including hip structural geometry and body composition, in a multi-ethnic population of postmenopausal women participating in the WHI study. The specific aims of this dissertation are to:

1) Investigate the association between fracture risk and RA in the entire WHI cohort (n=161,808). Hypothesizing that women reporting RA will have an increased fracture risk than women not reporting arthritis.
2) Assess bone strength and its longitudinal changes in women with RA in the WHI BMD sub-cohort (n=11,020). Hypothesizing that women reporting RA will have significantly lower bone strength and a greater loss over time than women not reporting arthritis.
3) Assess body composition and its longitudinal changes in women with RA in the WHI BMD sub-cohort (n=11,020). Hypothesizing that fat mass and lean mass will be different in women reporting RA compared to women not reporting arthritis, and that women reporting RA will lose more lean mass and gain more fat mass over time than women not reporting arthritis.
4) Assess the effect of age, ethnicity, and glucocorticoid use in the fracture, hip structural geometry, and body composition associations
5) Assess differences in characteristics in women reporting RA compared to those with medication validated RA.

Dissertation Format

The dissertation will first provide a review of the literature related to osteoporosis, bone strength, body composition, and RA. Methodology and background information on the WHI study will be presented next, followed by the additional background, methods, results, and discussion for the three main studies. The final chapter provides an overall dissertation conclusion and presents future direction for RA and osteoporosis research.

CHAPTER 2: REVIEW OF OSTEOPOROSIS

BONE BIOLOGY

Bone is a dynamic tissue and serves two primary functions: 1) mechanical integrity for locomotion and protection, and 2) mineral homeostasis (19). Bone is composed of two phases: inorganic matter and organic matter. The inorganic phase consists of hydroxyapatite crystals, which gives bone its strength. The organic phase is made up of predominantly type 1 collagen proteins and a variety of non-collagen proteins, which play a role in the biochemical properties and flexibility of bone (19).

There are two types of bone. The first, trabecular bone, consists of a network of rod and plate shaped trabeculae surrounding a bone marrow filled pore space (19). Trabecular bone is porous, and is found predominantly in the bones of the head and trunk, and along the inner regions of long bones. Cortical bone, or compact bone, is the second type. Cortical bone is not porous, and is typically found along the outer edges on bone, particularly long bones.

At the cellular level, bone is composed of three main cell types: osteoblasts, osteoclasts, and osteocytes. Osteoblasts are the cells responsible for bone formation. Molecular signals initiate preosteoblasts to differentiate into mature osteoblasts, which produce the bone matrix including hydroxyapatite and type 1 collagen. Osteocytes, or terminally differentiated osteoblasts, are encased in the mineralized matrix. Osteocytes are connected to each other via long cytoplasmic projections, and act as mechanosensors. Under mechanical strain, signals from osteocytes induce factors responsible for osteoblast proliferation or differentiation. Osteoclasts are the cells responsible for bone

resorption. Through attachment of its ruffled membrane to the bone surface, osteoclasts degrade bone by releasing enzymes from its many nuclei.

The bone formation and resporption process is known as bone remodeling, and maintenance of adequate bone mass requires a balance of resporption and formation. The aging process and/or the presence of certain conditions can result in an uncoupling of the remodeling process, leading to increased skeletal fragility. Osteoporosis is a condition of generalized skeletal fragility in which bone strength is sufficiently weak that fractures occur with minimal trauma (19).

DEFINING OSTEOPOROSIS

Osteoporosis is clinically defined based on bone mineral density (BMD). Dual energy X-ray absorptiometry (DXA) is currently the gold standard for easily and accurately measuring BMD. In simple terms, DXA is comprised of two X-ray beams with differing energy levels (20). Soft tissue, including skeletal muscle mass and fat mass, and bone tissue absorb both beams, and after subtracting out the soft tissue portion, BMD is estimated in g/cm^2 (20). DXA manufacturers provide estimates of total body and regionalized (hip and lumbar spine) BMD, and also converts the BMD estimate to a T-score. The T-score is the number of standard deviations a person falls above or below the mean BMD relative to the World Health Organization (WHO) reference group (21). The WHO reference population consists of the healthy Caucasian females between the ages of 20-29 who participated in the US's Third National Health and Nutrition Examination (NHANES III) survey (21). Sex, age, and racial-specific reference groups have also been

used to calculate Z-scores, which estimates how many standard deviations a person falls above or below the sex, age, or racial reference group being used. Based on epidemiologic fracture studies, the WHO set the osteoporosis diagnosis cutoff at a T-score of 2.5 standard deviations, or less, below the mean young normal group (T-score -2.5 or less) (21). The femoral neck region is most commonly used for the diagnosis of osteoporosis, but other regions including the lumbar spine and total hip, and in some cases, the distal 1/3 radius can be used (22).

Epidemiology of Osteoporosis

Osteoporosis affects 10 million people 50 years or older in the USA (1, 3, 23). In 2005, it was estimated that 13.7-20.3 billion dollars were spent on the direct medical costs of osteoporosis (3). Fractures are the most devastating outcome associated with osteoporosis, and in 2000, nine million new osteoporotic fracture occurred within the US (1). Typical osteoporosis related fractures include those of the spine, wrist, and hip. Hip fractures are the most serious fracture outcome of osteoporosis, and though they only represent 14% of the fracture cases, hip fractures account for 72% of the total medical costs spent on fracture in the USA (3).

Hip fractures are associated with a variety of adverse outcomes included increased pain, disability, and mortality (1). It was projected that hip fractures account for 1.53 million disability adjusted life years in women and 0.82 million in men (24). Johnell and Kanis also estimated excess mortality in women 70-74 years old to be 25 per 100,000

for hip fractures (24), and a recent meta-analysis showed that 10-45% of hip fracture cases die within the first year of fracture (2).

Risk factors for osteoporosis include age, and a variety of lifestyle, genetic, medical, and treatment factors (Table 1). Risk factors for osteoporosis and fractures may differ by race and ethnicity, and to assess racial and ethnic differences Cauley and colleagues examined risk factors for fracture by ethnicity within the WHI population (25). Differences in risk factors were found by ethnicity (Table 2), which is important for clinicians to consider in the treatment of osteoporosis.

Treatment of Osteoporosis

The National Osteoporosis Foundation (NOF) sets the clinical guidelines for the treatment of osteoporosis in the US. In 2005, the NOF considered it cost-effective to treat postmenopausal Caucasian women if they: a) had a prior vertebral or hip fracture, b) had a femoral neck T-score $\leq$-2.0 by DXA, or c) if they had low femoral neck BMD in the presence of one ore more risk factors (26).

Other international osteoporosis groups had similar BMD based treatment guidelines; however, many researchers began to question the heavy weighting of BMD in treatment guidelines. Studies assessing the predictive ability of BMD and the importance of other risk factors on fracture risk were performed; including an analysis of nine prospective population-based cohorts from Europe and Japan (27). The study evaluated how the addition of clinical risk factors to BMD altered fracture prediction, and the findings were validated in 11 other population based cohorts from Europe, US, and

Australia (27). The use of clinical risk factors alone was not able to better predict fractures than BMD alone, but the combination of BMD and clinical risk factors enhanced fracture prediction (27). With this information, the leaders in the osteoporosis field began to develop a new prediction tool.

FRAX®, the new WHO Fracture prediction tool, is a computer-based algorithm that provides the 10-year probability of major osteoporotic fractures; including hip, clinical spine, humerus or wrist fractures, and the 10-year probability of hip fracture alone after input of BMD and the major clinical risk factors identified and validated from the cohorts mentioned above (28, 29). The risk factors included are presented in table 3 (28, 29). Population specific FRAX® models have been developed for Austria, China, France, Germany, Italy, Japan, Spain, Sweden, Switzerland, Turkey, United Kingdom, and USA (30). The USA version allows for the input of ethnicity.

The 2008 NOF osteoporosis treatment guidelines incorporated the FRAX® model, and now treatment is considered cost-effective for men ≥ 50 years of age and postmenopausal women of all races with: "a) a vertebral or hip fracture, b) a BMD T-score ≤-2.5 at the femoral neck or spine, or c) low bone mass at the femoral neck or spine (T-score -1 to -2.5) if the 10-year hip fracture probability is ≥3% or the 10-year probability of major osteoporosis-related fractures is ≥20% (23)". Current FDA approved drugs for the prevention and treatment of osteoporosis includes bisphosphonates, calcitonin, estrogen therapy, selective estrogen receptor modulators (SERMs), parathyroid hormone, and recently a receptor activator of nuclear factor-kappa B (RANK) ligand monoclonal antibody (Table 4).

Table 1. Risk Factors for Osteoporosis and Fractures

Lifestyle Factors		
Low calcium intake	Vitamin D insufficiency	Excess vitamin A
High caffeine intake	High salt intake	Aluminum
Alcohol	Inadequate physical activity	Immobilization
Smoking	Falling	Thinness
Genetic Factors		
Cystic Fibrosis	Homocystinuria	Osteogenesis imperfecta
Ehlers-Danlos	Hypophosphatasia	Parental history of hip fracture
Gaucher's disease	Idiopathic hypercalciuria	Porphyria
Glycogen storage disease	Marfan syndrome	Riley-Day sundrome
Hemochromatosis	Mekes steely hair syndrome	
Hypogonadal States		
Androgen insensitivity	Hyperprolactinemia	Turner's & Klinefelter's syndromes
Anorexia nervosa and bulimia	Panhypopituitarism	Athletic amenorrhea
Premature ovarian failure		
Endocrine Disorders		
Adrenal insufficiency	Diabetes mellitus	Thyrotoxicosis
Cushing's syndrome	Hyperparathyroidism	
Gastrointestinal Disorders		
Celiac disease	Inflammatory bowel disease	Primary biliary cirrhosis
Gastric bypass	Malabsorption	GI surgery
Pancreatic disease		
Hematologic Disorders		
Hemophilia	Multiple myeloma	Systemic mastocytosis
Leukemia and lymphomas	Sickle cell disease	Thalassemia
Rheumatic and Autoimmune Diseases		
Ankylosing spondylitis	Lupus	Rheumatoid Arthritis
Misc. Conditions & Diseases		

Alcoholism	Emphysema	Muscular dystrophy
Amyloidosis	End stage renal disease	Parenteral nutrition
Chronic metabolic acidosis	Epilepsy	Post-transplant bone disease
Congestive heart failure	Idiopathic scoliosis	Prior fracture as an adult
Depression	Multiple sclerosis	Sarcoidosis
	Medications	
Anticoagulants	Cancer chemotherapeutic drugs	Gonadotropin releasing hormone agonists
Anticonvulsants	Cyclosporine A and tacrolimus	Litium
Aromatase inhibitors	Depo-medroxyprogesterone	Barbituates
glucocorticoids		

*Clinician's Guide to Prevention and Treatment of Osteoporosis. (23)

Table 2. Significant Risk Factors for Osteoporotic Fractures by Ethnicity*

	White	African American	Hispanic	Asian	American Indian
Age	X		X	X	
Years since menopause	X				
>High School vs. ≤ High School	X	X			
≥College vs. ≤ High School	X	X			
Living with partner	X				
Parental Fracture	X				
Weight	X				
Height	X		X		
Daily Caffeine intake	X				
Current Smoking	X				
Fracture ≥55 years	X	X	X	X	X
>2 Falls	X	X		X	
Current HT	X				
HT ≥ 5 years	X				
Corticosteroid use >2 years	X		X		
Sedative/antiolytics use	X				
History of Arthritis	X		X		
Depression	X				
≥Good self-reported health status vs. Fair/poor	X				
Parity					
1				X	
2-4	X				
≥5				X	

***adapted from Cauley, 2007 (25)**

Table 3. Clinical Risk Factors used in FRAX®

Age
Body Mass Index (BMI)
Previous fragility fracture
Parental history of hip fracture
Current tobacco Smoking
Ever long-term use of oral glucocorticoids
Rheumatoid arthritis
Other causes of secondary osteoporosis
Alcohol consumption ≥3 units/day
Femoral neck BMD

(Kanis,2007)(27)

Table 4. FDA-approved Osteoporosis Agents*

Bisphosphonates			
Generic Name	**Brand Name**	**Approved for…**	**3 Year Fracture Reduction**
Alendronate	Fosamax®	- Postmenopausal osteoporosis - Treatment of osteoporosis in men - Treatment of glucocorticoid-induced osteoporosis	- 50% reduction in spine and hip fractures in those with previous vertebral fracture - 48% reduction of incident vertebral fractures in those without prior vertebral fracture
Ibandronate	Boniva®	- Treatment and prevention of postmenopausal osteoporosis	- 50% reduction of incident of vertebral fractures
Risedronate	Actonel®	- Treatment and prevention of postmenopausal osteoporosis - treatment of glucocorticoid-induced osteoporosis	- 41-49% reduction in vertebral fractures - 36% reduction of non-vertebral fractures
Zoledronic Acid	Reclast®	- Treatment of postmenopausal osteoporosis	- 70% reduction of incident vertebral fractures - 41% reduction of hip fractures - 25% reduction on non-vertebral fractures

Calcitonin			
Generic Name	**Brand Name**	**Approved for…**	**3 Year Fracture Reduction**
Calcitonin	Miacalcin® Fortical®	- Treatment of osteoporosis in women at least 5 years postmenopausal	

Estrogen/Hormone Therapy			
Generic Name	**Brand Name**	**Approved for…**	**3 Year Fracture Reduction**
Estrogen Therapy	Climara® Estrace® Estraderm® Estratab®	- Prevention of osteoporosis	

Hormone Therapy	Ogen® Ortho-Est® Premarin® Vivelle® Activella® Femhrt® Premphase® Prempro®	- Prevention of osteoporosis	Prempro - 34% reduction of hip fractures - 23% reduction of other fractures

Selective Estrogen Receptor Modulators (SERMs)			
Generic Name	**Brand Name**	**Approved for…**	**3 Year Fracture Reduction**
Raloxifene	Evista®	- Prevention and treatment of postmenopausal osteoporosis	- 30% reduction in vertebral fractions with a prior vertebral fracture - 55% reduction in vertebral fractures in patients without a prior vertebral fracture

Parathyroid Hormone			
Generic Name	**Brand Name**	**Approved for…**	**3 Year Fracture Reduction**
Teriparatide	Forteo®	Treatment of postmenopausal osteoporosis; anabolic agent	- 65% reduction in vertebral fractures - 53% reduction in non-vertebral fractures

RANK-ligand Antibody			
Generic Name	**Brand Name**	**Approved for…**	**3 Year Fracture Reduction**
Denosumab	Prolia™	Treatment of postmenopausal osteoporosos	- 68% reduction in vertebral fractures - 40% reduction in hip fractures - 20% reduction in non-vertebral fractures

*adapted from Clinician's Guide to Prevention and Treatment of Osteoporosis (23)

CHAPTER 3: BONE STRENGTH

Osteoporotic fractures occur when the strength of the bone is less than forces applied to it (31). Strength is determined by the material and structural properties of the bone. Material properties include mineralization density and cortical porosity, which influence the amount of stress required to result in and the characteristics of a fracture (32). Material properties can only be evaluated by specialized biopsy methods, and are not routinely performed in the general population. Structural properties include microarchitecture and geometry (33). Because low BMD is strongly correlated with increased fracture risk, BMD is commonly measured as a marker of bone strength. However, BMD is not a direct measure of either structural geometry or tissue material properties.

Various methods have been used to measure structural changes at the macroscopic level while attempting to interpret their implications in the mechanical strength of bone. Quantitative computed tomography (QCT) has been used to measure BMD in addition to micro architecture (31); however, QCT is very expensive and requires more radiation that other methods. DXA is the most widely used method of densitometry, making it the perfect tool to not only measure BMD, but selected structural variables also.

Principles of Hip Strength Analysis

In the early 90's Beck and colleagues developed a hip strength analysis (HSA) program, which utilizes DXA images to extract geometric variables to produce strength

estimates (34). The group focused on the hip given that it is the most adverse site of fractures. Using the mechanical stress theory, the HSA program combines mechanical engineering principles with bone density data. Mechanical stress of long bones, such as the femur, includes bending and axial compressions (32, 34). The magnitude of stress depends on the surface area of the bone and the distribution of stress along the bone (32, 34). At three femur regions (narrow neck, intertrochanteric, and shaft (Figure 1), the HSA program estimates conventional BMD, cross-sectional area (CSA), center of mass, outer diameter, cortical thickness, cross-section moment of intertia (CSMI), neck shaft length, and neck shaft angle of each cross-section (Table 5) (32, 34). Two strength estimates, section modulus and buckling ratio, are calculated at each of the three regions based on the parameters. Section modulus, an index of bending strength, is calculated by dividing the CSMI by the distance from the center of mass is at its maximum (32, 34). Buckling ratio is a crude index of susceptibility to local bucking under bending loads, and is calculated by dividing the radius of cross-section by the mean cortical thickness (32, 34). In early work with HSA, Dr. Beck found that changes in femoral neck geometry were highly correlated with bending and compression strength(34).

Treatments Effects on Bone Strength

With the gain in HSA popularity, research has been conducted on various treatment agents to see how they influence structural geometry. The effect of raloxifene, a selective estrogen receptor modulator (SERM) shown to reduce the incidence of new vertebral fractures in postmenopausal women, was studied on hip strength in a study of

more than 7,500 postmenopausal women. It was found that raloxifene treatment increased both BMD and structural strength (one percent average increase) compared to the placebo group (35). The structural effect of teriparatide, a parathyroid hormone derivative and anabolic osteoporosis agent, was also studied. The participants were randomized to receive subcutaneous injections of two doses of teriparatide (20ug or 40ug) or placebo injections, and the study found a significant treatment effect on bone mass and bone structure improving the mechanical strength and stability at common fracture sites (36).

Structural improvements have been shown with bisphosphonate therapy (37-40). In a subset of participants from the Fosamax Actonel Comparison Trial, structural effects were evaluated on women taking risendronate or alendronate for over two years (37). Strength parameters improved in all femoral regions (narrow neck, intertrochanteric, and shaft), with greatest effect seen at the intertrochanteric regions and larger effects in those taking alendronate (37).

Specifically in the WHI, the effect of hormone therapy (HT) and calcium and vitamin D (CaD) supplementation on hip strength has been evaluated. Women on active HT treatments, either conjugated equine estrogen or estrogen plus progestin, had an almost 4% increase in hip strength compared to controls, with a greater effect of HT on the intertrochanteric regions (41). CaD also showed positive benefits on hip strength within the WHI population, with an average 1-2% increase in hip strength (Jackson unpublished data). Although the HT study showed greatest effect at the intertrochanteric

region, the CaD study found the greatest treatment effect in the narrow neck region (Jackson unpublished data).

Hip Strength and Fracture

As indicated above, hip strength can be improved with a variety of treatments; however, HSA was developed with the goal to ultimately improve individual fracture assessment. Rivadeneira and colleagues examined hip strength parameters among hip fracture cases and controls enrolled in the population based cohort of the Rotterdam Study, and found that in both men and women, hip fracture cases had significantly lower indices of strength than controls (42). Similarly, Kapotge showed that buckling ratio, the index of susceptibility to local cortical buckling under compressive loads, was elevated in hip fracture cases compared to controls (43), showing that structural instability is related to fractures.

Several researchers have evaluated the addition of structural parameters to conventional BMD measurements on the prediction of hip fracture. Before the wide use of HSA, Crabtree and colleagues used a case-control study of recent female hip fracture patients and population based controls to assess if adding hip structural parameters to conventional BMD measurements provided any added benefit to hip fracture prediction. They found that their measure of compressive stress provided more information to fracture risk than femoral neck BMD alone (44). Recently, LaCroix and colleagues performed similar analyses using HSA measurements in the WHI bone density cohort (45). The group found that even though many of the structural measures were highly

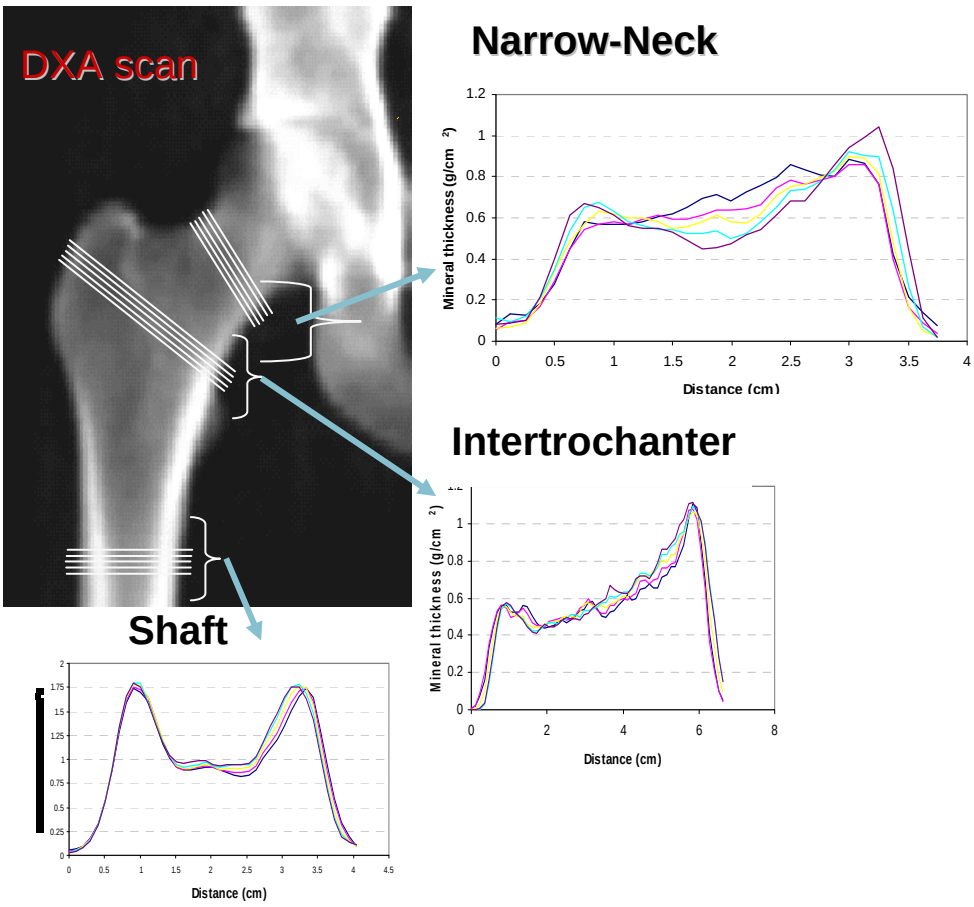
correlated to BMD, outer diameter width at the intertrochanter region, was independently associated with a significant increase risk for hip fracture; highlighting the importance of having both material and structural measures in the examination of fracture risk.

Table 5. Variables Estimated by Hip Structural Analysis

Measure	Unit	Calculation	Definition
Center of Mass			
Cross-sectional Area (CSA)	cm^2		Bone surface area
Cross-sectional moment of inertia (CSMI)		Integration of the products of incremental areas and the square of their distance from the neutral axis	Index of structural rigidity
Cortical Thickness	cm	Pixel g/cm2 value divided by effective density of fully mineralized bone	
Outer Diameter	cm		The distance from the ends of the cross-section
Neck Shaft Length	cm		
Neck Shaft Angle	degree		
Section Modulus	cm^3	CSMI divided by the distance of the pixel from the center or mass	Index of bending strength
Buckling Ratio		Outer diameter divided by the cortical thickness	An index of resistance to local cortical buckling

*Adapted from (32, 34)

Figure 1: Femoral Cross-Sections used to Extract Structural Geometry



CHAPTER 4: BODY COMPOSITION AND BONE

SKELETAL MUSCLE AND BONE

As first noted by Frost, strain on bones is related to both aspects of bone strength (mass and geometry) (46). The mechanostat theory proposes that "increasing maximal muscle force during growth or in response to increased loading will affect bone mass, size, and strength predictably and correspondingly" (17). Strain, or mechanical force, on bone is produced through gravitational forces (impact with the ground) and/or muscle contractions (47). Most of the work on the relationship between muscle and bone has been done on children and adolescents during growth periods and in populations with limited muscle forces on bone (immobilization, patients on bed rest, and astronauts) (17).

Increases in muscle mass, body mass, and growth have been said to add to the maximal forces responsible for adapting bone structure and strength (17). For example, children without substantial muscle strain have reduced bone mass, and altered bone shape of the long bones (17). In spinal cord injury patients, immobilization leads to reduced muscle mass, muscle force, and muscle activity; all which are detrimental to bone mass (17). For example, Eser and colleagues noted that spinal cord patients have rapid decreases in volumetric BMD of trabeculae and decreases in cortical thickness after injury (48).

Exercise is a key component of increasing muscle mass and strain on bone. However, studies have shown that muscle size alone is not a good indicator of muscle strain needed to stimulate a response in bone (17). For example, athletes participating in low impact activities, such as cycling or swimming, tend to have larger muscle mass, but

lower BMD than controls (17). Athletes participating in high impact sports, such as volleyball or gymnastics, tend to have greater BMD than controls even when matched to individuals with similar values of muscle mass. Individuals with a greater body weight may have a larger absolute value of muscle mass, but the increase in muscle may not result in similar increases in bone mass or strength.

Fat Mass and Bone

Larger body weight is thought to be protective against fracture risk. In a meta-analysis of 10 European osteoporosis cohorts, a reduction in fracture risk was found in both men and women per unit increase in BMI (49). For any type of fracture and all osteoporotic fractures combined, those with a BMI of 35 kg/m^2 had a 15% and 25% reduction in fracture risk compared to those with a BMI of 25 kg/m^2 (49), suggesting that body weight protects against fractures. However, when the analyses were adjusted for BMD, the relationship between BMI and fracture risk disappeared (49). The adjusted results suggest that increases in body fat does not equate to increases in bone strength. Travison and colleagues reported that lean mass and not fat mass, is associated with various HSA derived variables of femur strength (50). Similarly Beck and colleagues reported that after adjusting for body weight, femoral BMD and other structural geometry indices decreased as BMI increased (51), suggesting that fat mass reduces bone strength.

Several theories have been proposed relating fat mass to bone strength. Adipocytes, or fat cells, originate from mesenchymal stem cells, which are also the precursor cell for osteoblasts (52). It has been hypothesized that increases in adipocytes

number with increases in fat mass takes places at the expense of osteoblasts since they share the same precursor cell (52). Decreases in osteoblast number is one explanation of the reduced bone formation seen in osteoporosis. The aging process also reduces the proteins and growth factors needed to differentiate mesenchymal stem cells into osteoblasts, and without the proper molecular factors, stem cells revert to adipocyte instead of obsteoblasts, further reducing bone mass (52). In addition to soft tissue deposits, adipocytes also find their way to the bone marrow, resulting in fatty infiltrates in the bone, further compromising mass and strength (52).

SARCOPENIA

As identified above, muscle mass and strain are very important in bone health. Cross-sectional studies of body composition have shown that individuals lose between 1-6% of muscle mass per decade between ages 45-80 years (53, 54). Sarcopenia is the term given to age related decline in muscle mass and strength, and is associated with many adverse outcomes such as osteoporosis and cardiovascular health. Baumgartner et al. defined sarcopenia as appendicular skeletal mass/height^2 (kg/m^2) less than two standard deviations (SD) below the average young adult value (53). Using this method, they found that the prevalence of sarcopenia was between 13-24% in elderly Hispanic and non-Hispanic White men and women under the age of 70 years, and increased to over 50% in those over 80 years (53).

Newman and colleagues took a different approach, and defined sarcopenia as those with residuals in the 20th percentile or below after regressing appendicular lean

mass on height and absolute fat mass (55). Using the Baumgartner method, roughly 50% of the male and female participants in the Dynamics of Health, Aging and Body Composition (Health ABC) study with a BMI of less than 25 kg/m^2 were considered sarcopenic, whereas only 33% of the men and 23% of the women in that BMI category were considered sarcopenic under the residual definition (55). The residual method also identified 12% of men and 14% of women with a BMI greater than 30 kg/m^2 as sarcopenic, whereas the Baumgartner method did not identify any (55).

Sarcopenia, using either definition, is associated with increased disability, functional incapacity, falls, and osteoporosis (54, 56, 57). The relationship between osteoporosis and body composition in older populations has been mixed in the literature. Capozza and colleagues found that low lean mass, low bone mineral content, and lean mass index scores were associated with fractures in their population of postmenopausal women, and using Baumgartner's method, a higher prevalence of sarcopenia was found in osteoporotic women than women with low or normal BMD (58). Similarly, Lima et al found that women with sarcopenia were more likely to have low BMD than controls (59). However, Walsh and colleagues did not find a statistical association between sarcopenia and osteoporosis (60). Similarly, Gillette-Guyonnet et al. found higher prevalence of sarcopenia in osteoporotic women, but no statistical association between the two (61).

SARCOPENIA OBESITY

As fat mass has been shown to be associated with decreased bone strength, researchers have begun to assess the relationship between obese individuals with low

levels of lean mass, or sarcopenic obese individuals. There are several working definitions for sarcopenia obesity. Baumgartner added percent fat to his sarcopenia definition to define sarcopenia obesity as those with an appendicular skeletal muscle index two SD below the young reference and had greater than 27% fat in men and 38% fat in women (62). Davison and colleagues defined sarcopenia obesity as individuals in the upper two quintiles of body fat and the lower three of muscle mass (63).

Regardless of definitions used, sarcopenic-obese men and women have a significantly greater chance of disabilities and other adverse health outcomes than their non obese or non-sarcopenic counterparts. For example, Rolland et al, studied the association between sarcopenia and obesity on physical function, and found that the individuals who were only sarcopenic and not obese and the individuals who were obese and not sarcopenic had 50% more difficulty in climbing stairs than normal controls, but the level of difficulty was nearly 3.5-fold higher those who were sarcopenic and obese compared to controls (64). Recently, Stephen and Janssen found increased risk for cardiovascular disease in the sarcopenic-obese groups, but not in the obese or sarcopenic groups alone (65). Very few studies have been conducted looking at the association between sarcopenic obesity and osteoporosis or osteoporotic fractures. In a small study of 27 obese postmenopausal women, Aubertin-Leheudre et al, found no differences in fat mass between the three difference sarcopenia categories (non-sarcopenia, sarcopenia class I, sarcopenia class II), and suggested that fat mass helped in the preservation of BMD in the sarcopenic women (66); however, this association would need to be tested in a larger population.

CHAPTER 5: RHEUMATOID ARTHRITIS AND ITS RELATIONSHIP WITH OSTEOPOROSIS

EPIDEMIOLOGY OF RHEUMATOID ARTHRITIS

Rheumatoid Arthritis (RA) is a multi-system disorder characterized by chronic destructive synovitis, associated with substantial adverse health consequences (4). No "gold standard" for assessing RA prevalence has been established; however Lawrence and colleagues have estimated prevalence to be about one percent in the general population (67, 68). An examination of NHANES-III data showed that the prevalence of self-reported RA in those 60 years and older was around two percent, with a greater prevalence in women, persons older than 70 years, those less educated, and Mexican Americans (6).

The etiology of RA is unknown; however, several environmental and genetic risk factors are known to increase the incidence and possibly the severity of symptoms in RA. Several studies in twins and first degree relatives have demonstrated that there is a strong genetic association in RA. Through advancing genetic technology, clearer associations with human leukocyte antigen genes and RA have been made, as well as the identification of several single nucleotide polymorphisms that are potentially associated with RA (69, 70).

Other factors related to RA include gender, age, hormonal factors, and lifestyle factors such as BMI and smoking status (4). The female to male ratio among RA patients is 3:1, and the condition most commonly presents within the 4^{th}-6^{th} decade of life (4). Smoking has been implicated in disease activity, and it was shown that compared to past

or never smokers, current smokers with newly diagnosed RA had more prominent disease presentation features, higher number of tender and swollen joints, and a higher Larsen score, a tool used to assess disease damage from radiographs (71).

RA AND BONE LOSS

Three major forms of bone loss have been described in RA: 1) Focal articular bone erosions, 2) periarticular bone loss, and 3) generalized osteopenia in both the appendicular and axial skeleton (72). Because the pathology behind generalized bone loss varies widely, it is one of the most frequently studied types of bone loss in RA. In the past decades, several studies have used a variety of methods to investigate generalized bone loss in patients with RA. The study populations ranged from 19 to 195 patients, including both pre and postmenopausal women and men with RA. BMD was assessed at several sites: the distal radius, proximal femur, lumbar spine, femoral neck, and metacarpals. BMD was lower in the RA patients compared to their controls at most sites. In studies that included both the lumbar spine and femoral neck, it was found that a greater loss of bone mass was seen in the hip regions compared to the spine regions (73, 74). Factors that were found to magnify bone mass loss included: disease activity, reduced motility due to functional impairment, and use of corticosteroids (73-78).

Studies performed within the past few years have incorporated the strength of longitudinal study designs, as well as increasing the sample size to as many as 925 RA patients. However, the study results were similar to those in the previous years. Lodder and colleagues found that those with more severe disease measured by Larsen score had

significantly greater bone loss at the hip (13). In a study by Kroot and colleagues, postmenopausal women with low levels of physical activity were at the highest risk of losing bone mass (12). A cross-sectional analysis of patients from the Oslo County RA register showed that BMD of the total hip was significantly reduced by 3.7%, 6.0%, and 8.5% in RA patients age 40-49, 50-59, and 60-70 years compared to controls (79). Factors that predicted bone mass loss included older age, low weight, current use of corticosteroids, and higher Modified Health Assessment Questionnaire (M-HAQ) disability score (79). From these and other studies we have learned that postmenopausal RA women have lower BMD at several sites, including the lumbar spine, mid-radius, and calcaneus, when compared to women without arthritis (80). Postmenopausal women with RA have significantly greater annual bone loss at several sites compared to control populations, and osteoporosis in RA is characterized by marked bone loss in the peripheral bone compared with the lumbar vertebrae (80); making a study in the participants of the WHI an appropriate cohort to examine the association between RA and factors related to osteoporotic fractures.

RA and Fracture Risk

Several studies have documented that RA is associated with decreases in bone mass and higher levels of bone resorption factors, and it was important to determine how those factors correlated with fracture risk. A population-based study performed by Hooyman and colleagues, followed female patients with RA over a 25 year period, and found a significantly increased risk for pelvic [Hazard Ratio (95% Confidence Interval)]

[2.56 (1.32, 4.47)] and proximal femur [1.51 (1.01, 2.17)] fractures (15). Similarly, Spector and colleagues found that the rate of vertebral fractures in women with RA was twice that of the controls (81). Researchers in Finland found an age and sex adjusted risk ratio of 3.26 (2.26, 4.70) for hip fractures for patients with RA, with the highest risk in those 64 years and younger (16).

Increases in fracture risk have also been shown in those RA patients who are on corticosteroid therapy. Studies show an increased risk of vertebral fractures [Odds Ratio (95% Confidence Interval)] [1.42 (0.24, 8.32)] and hip fractures (OR=2.8 (1.2, 6.2)) in RA patients on corticosteroid therapy (82, 83). However, it is not clear whether corticosteroids affect the risk of fracture directly, or it is that those patients prescribed corticosteroids are more likely to have advanced disease or be functionally limited (84). Whether disease induced or therapy induced, it is well noted that those with RA experience loss of bone mass and increases in fracture risk.

RA and Body Composition

Muscle wasting, or cachexia, is a known phenomenon in RA. Due to the chronic inflammation experienced in RA, decreases in cell size result in decreases of lean body mass (85). Fat mass is either maintained or increases in the presence of stable body weight (5, 18). Several measurement techniques have been used in studies of body composition in RA patients, including anthropometric methods, urinary creatinine excretion, bioelectric impedance (BIA), and imaging techniques (85). DXA has been widely used, and small studies examining body composition in RA patients found that

upper arm fat mass was similar to controls, but that over half of the RA patients fell into the lowest tenth percentile for upper arm muscle mass (86). Other studies focusing on lean body mass have found that RA patients have lower lean body mass than controls (85). Specifically in DXA, lean body mass estimates ranged from 0% (87, 88) to 12% (89) reduction in RA patients compared to controls.

Body fat has also been examined in RA patients compared to controls in several studies (85). Westhovens and colleagues found that lean body mass was lower and percent fat was higher at all measured sites in the RA group compared to the control group (90). In a British RA population, Stavropoulos-Kalinoglou found that for a given BMI, RA patients had 4.3% more fat mass, measured by BIA, than controls, and suggested that obesity cutoffs be lowered to a BMI of 28 kg/m^2 instead of 30 kg/m^2 (91). Cardiovascular disease, a common outcome of RA (92), is associated with increases in abdominal fat (93), and studies found that RA patients have a shift in fat from appendicular sites of the arms and legs to DXA identified trunk region (90, 94).

Sarcopenia, or age-related muscle loss, has also been assessed in RA patients. Giles and colleagues conducted a body composition study in 189 RA patients utilizing the current sarcopenia definitions, and found that the female RA patients had a higher mean total fat, percent fat, and fat mass index than controls, but no statistical difference was seen in measures of lean mass. The group also found that the percentage of women falling into the sarcopenic, higher percent fat, and sarcopenic obesity categories was higher in the RA group than the non-RA group (95).

Both cachexia and sarcopenia are associated with poor disease outcomes, and Giles followed up their initial evaluation on body composition in RA to see how it influence disability. Using the Health Assessment Questionnaire (HAQ), they found that higher appendicular fat mass was associated with a higher HAQ score (indicating more disability), and inversely, higher appendicular lean mass was associated with lower HAQ scores (indicating less disability) (96). This effect was more prominent in women than men, but men followed a similar trend.

Disease activity is highly correlated with disability, and a study by Elkan and colleagues found that percent fat mass was highly positively correlated with erythrocyte sedimentation rate (ESR), a marker of inflammation, and in the multivariate analyses, found that high ESR was significantly related to low fat free mass and high fat mass (97).

SUMMARY

RA is associated with many adverse outcomes, including osteoporosis. RA patients have reduced BMD and increased fracture risk compared to healthy controls; however, there have been no studies assessing the structural properties in this population. It is also clear that RA affects body composition, but most of the studies are cross-sectional and do not assess the association between RA and changes body composition over time. In most aging populations, loss of skeletal muscle is correlated with loss of bone mass, however in RA; few studies have assessed how changes in body composition are related to osteoporosis risk.

Very few studies have also assessed the racial and/or ethnic differences on RA and osteoporosis risk or changes in body composition. This is the first longitudinal study on hip structural geometry in postmenopausal women with RA, in addition to one of the first longitudinal studies of body composition in a multi-ethnic population of women with RA. Knowing the structural dynamics of bone over time as well as how RA alters body composition, tailored interventions against decreases in bone strength can be developed for this high fracture risk population.

CHAPTER 6: WOMEN'S HEALTH INITIATIVE STUDY

The Women's Health Initiative (WHI) is a nationwide study that investigated the risk factors and preventive strategies of the major contributors to morbidity and mortality in postmenopausal women: including heart disease, breast and colorectal cancer, and osteoporotic fractures (98). The WHI recruited 161,808 postmenopausal women aged 50 to 79 from 40 centers across the country to participate in the clinical trials (CT) component; including the postmenopausal hormone therapy trial (HT), dietary modification trial (DM), and the calcium and vitamin D trial (CaD); or the observational study (OS) (Table 6). In summary recruitment activities involved mass mailings, community presentations, and advertisements in local and national newspapers (99). To increase generalizability, the WHI designated 10 of the 40 clinical centers to serve as minority recruitment centers. In addition to standard recruitment activities, staff at these centers, frequented churches and organizations that catered to the population of interest.

The overall inclusion criteria included being postmenopausal between the ages of 50-79 years, willingness to provide written informed consent, and an agreement to reside in the area for at least 3 years after enrollment. Women with any medical condition with a predicted survival of less than 3 years, alcohol or drug dependency, mental illness, dementia, or actively participating in another randomized intervention trial were generally excluded from the WHI (99). Inclusion and exclusion criteria differed slightly for each study component as summarized in tables 7-8.

A myriad of health information was self-reported by the participants at baseline and periodically throughout the study depending on component. A description of the

questionnaires and frequency of completion can be found in Appendix A. Anthropomentric measures such as height, weight, and waist to hip ratio was measured by clinic staff using standard procedures. Blood was drawn on each participant at baseline and again periodically throughout the study based on component (Appendix A). Additional biomarkers related to safety, adherence, or outcomes were measured on a 6% sub-sample of CT participants.

The primary outcomes of the study were related to breast and colorectal cancer, coronary heart disease, and osteoporotic fractures. Primary and secondary outcomes for each study component can be found on table 9.

Baseline Demographics of WHI

The mean baseline age ± SD of the participants was 63.2 ± 7.2 years. Overall 33% of women were between 50-59, 45% between 60-69, and 22% between 70-79 years. The majority of the participants were non-Hispanic White (82.5%), with 0.4% of the women representing American Indians, 9.0% African American, 2.6% Asian, 4.0% Hispanic White, and 1.1% other race or ethnicity. The participants were well educated with approximately 40% of the women having a college degree or higher. Overall, the participants were heavier than the general population with 29.5%, 34.9%, 33.8% in the normal weight, overweight, and obese categories. Perceived health status was overall high in the participants with 89.2% having rated their health status at good, very good, or excellent; and only 10.0% rating it fair or poor.

Defining Arthritis Within the WHI

The WHI health assessment form was used to identify arthritis status at baseline. The participants were asked, ‘‘Did your doctor ever tell you that you have arthritis?’’ with responses of yes or no. Women responding “yes” were then asked ‘‘What type of arthritis do you have?’’ with responses of “rheumatoid arthritis” and “other/do not know”. Women not reporting arthritis were categorized as non-arthritic controls. Women reporting RA were placed in the self-reported RA group, and women selecting “other/do not know” category were placed in the osteoarthritis (OA) category.

Medication Validation of Self-Reported Rheumatoid Arthritis Status

Using the method of Walitt and colleagues (100), a probable RA group was defined to include those women who reported RA and one or more of the following commonly used anti-rheumatic agents at baseline: methotrexate, gold, biologic anti-TNF agents, leflunomide, cyclophosphamide, azathioprine, cyclosporine, tacrolimus, hydroxychloroquine, minocycline, sulfasalazine, and glucocorticoids (Table 10).

Table 6. Components of the Women's Health Initiative Study (98)

	HT	DM	CaD	OS
Arm	n=27347	n=48,835	n=36,282	n=93,676
Intervention	E-alone: n=5,310 E+P: n=8,506	n=19,541	n=18,176	-
Control	E-alone: n=5,429 E+P: n=8,102	n=29,294	n=18,106	-

HT: Hormone trial; DM: Dietary modification trial; CaD: Calcium & Vitamin D supplementation trial; OS: Observational study; E-alone: Estrogen alone; E+P: Estrogen plus progestin

Table 7. Inclusion Criteria of the Women's Health Initiative (99)

Component	Inclusion Criteria
CT & OS	• 50-79 years of age • Postmenopausal o If age ≥55, no menstrual period for at least 6 months o If age 50-54, no menstrual period of at least 12 months • Ability and willingness to provide written informed consent • Intention to reside in area for at least 3 years

CT: Clinical Trial; OS: Observational Study

Table 8. Exclusion Criteria of the Women's Health Initiative (99)

Component	Exclusion Criteria
CT & OS	• Competing risk: o Any medical condition with predicted survival of <3 years • Adherence or retention reasons: o Alcohol or drug dependency o Mental Illness, including severe depression o Dementia o Active participation in other randomized intervention trial
CT	• Competing risk: o Any invasive cancer in previous 10 years o Breast Cancer at any time o Mammogram or CBE findings supicious of break cancer o MI in previous 6 months o Stroke or TIA in past 6 months o Chronic hepatitis or severe cirrhosis • Safety Reasons: o Severe hypertension (systolic BP >200 mmHG or diastolic BP>105mmHg o Severely underweight (BMI<18 kg/m2) o Hematocrit <32% o Platelets <75,000 cells/ml o Current use of oral daily corticosteroids • Adherence or Retention Reasons: o Unwilling to participate in baseline or follow-up examination components
DM	• Adherence or Retention Reasons: o Special dietary requirements incompatible with the intervention (ex celiac sprue) o On a diabetic or low salt diet o Gastrointenstional conditions contraindicating a high fiber diet o Type 1 diabetes o Olorectal cancer at any time o Routinely eat ≥10 meals per week prepared out of the home o Unable to keep a 4-day food record o FFQ percent calories from fat <32% o FFQ energy intakes <600 or >5000 kcal o Previous bilateral prophylactic mastectomy
HT	• Safety Reasons: o Endometrial cancer at any time o Endometrial hyperplasia o Malignant melanoma at any time

	○ History of pulmonary embolism or deep vein thrombosis ○ Previous osteoporosis-related fracture being treated with hormones ○ History of bleeding disorder requiring transfusion ○ History of hypertriglyceridemia ○ Currently take anticoagulants ○ Current on tamoxifen ○ Abnormalities in baseline pap smear, pelvic exam, or pelvic ultrasound • Adherence or Retention Reasons: ○ Severe menopausal symptoms that would make placebo treatment intolerable ○ Inadequate adherence to placebo run-in ○ Unable or unwilling to discontinue use of PHT or testosterone ○ Refusal to have baseline endometrial aspiration
CaD	• Safety Reasons: ○ History of renal calculi or hypercalcemia ○ Current use of oral corticosteroids or calcitriol ○ Intention to continue taking ≥600 IUs of vitamin D per day

CT: Clinical Trial; OS: Observational Study; HT: Hormone trial; DM: Dietary modification trial; CaD: Calcium and vitamin D trial; BMI: body mass index; BP-Blood pressure; CBE: Clinical breast exam; FFQ: Food frequency questionnaire; TIA: Transient ischemic attack; IU: International unit

Table 9. Women's Health Initiative Clinical Trial and Observation Study Outcomes (101)

Outcome	PHT	DM	CaD	OS
Cardiovascular				
Coronary heart disease	1°	2°	x	x
Stroke	2°	2°	x	x
Congestive heart failure	2°	2°	x	x
Angina	2°	2°	x	x
Peripheral vascular disease	2°	2°	x	x
Coronary revascularization	2°	2°	x	x
Venous thromoembolic disease				
Pulmonary embolism	2°	x	x	x
Deep vein thrombosis	2°	x	x	x
Total Cardiovascular	2°	2°	x	x
Cancer				
Breast	2°	1°	2°	x
Colorectal	x	1°	2°	x
Endometrial	2°	2°	x	x
Ovarian	2°	2°	x	x
Total Cancers	2°	2°	2°	x
Fractures				
Hip	2°	x	1°	x
Other fractures	2°	x	2°	x
Total fractures	2°	x	2°	x
Other				
Diabetes mellitus requiring therapy	x	2°	x	x
Death from any cause	2°	2°	2°	x

1°-primary outcome; 2°-secodary or safety outcome; x-ascertained

Table 10: Medications Used to Validate Rheumatoid Arthritis

Validation Medications	Therapeutic Class Code	Agents included
Anti-Rheumatics		
	662000	Gold Compounds
	662500	Antirheumatic Antimetabolite
	662700	Anti-TNFα Monoclonal Antibodies
	662900	Soluble TNF Receptor Agents
	663000	Misc. Antirheumatic
Cyclophosphamide	211010	
Glucocorticoids	221000	
Hydroxycholoroquine	130000	
Immunosuppressant		
	907840	Tacrolimus
	994020	Tacrolimus
	994040	Cyclosporine
	994060	Azathioprine
Methotrexate	213000	
Minocycline	040000	
Sulfasalazine	080000	
	525000	

CHAPTER 7: THE ASSOCIATION BETWEEN RHEUMATOID ARTHRITIS AND FRACTURE

INTRODUCTION

The first aim of this dissertation was to test the association between RA and fracture in the participants of the WHI. Arthritis, in general, is one of the largest public health concerns for aging populations. Direct and indirect costs attributable to arthritis and other rheumatic conditions have been estimated to total $128 billion (102), and the number of individuals diagnosed is expected to increase an average of 16% by year 2030 (103). RA affects approximately one million adults (67), whereas OA is estimated to affect 25 million adults in the United Sates (104). Osteoarthritis (OA) patients are often used as a comparison population in RA fracture studies as OA is not typically associated with fractures. Previous studies have associated OA as a "protective" factor for fracture (105-107), or have shown no increased or reduced risk in fractures among OA cases (108, 109). However, recently, a few studies have found an increased risk of fracture in OA patients (110, 111).

If arthritis, particularly OA, is associated with an increased risk of fractures, then the increasing arthritis prevalence would indicate a potential increase in fracture outcomes and associated complications. The primary goal of this study is to investigate fracture risk in a group of multi-ethnic postmenopausal self-reported arthritis cases compared to non-arthritic controls, with the hypothesis that women reporting RA have a higher fracture risk than women reporting OA and women without arthritis. This study will also test if the fracture association is modified by ethnicity or glucocorticoid use.

METHODS

Study Population

The entire WHI cohort (n=161,808) was used for this prospective analysis of arthritis and fracture. Arthritis status, was self-reported by participants at baseline, and incident fractures were reported over the follow-up period. Based on the previously described methodology (p.49), the arthritis exposure variables for this study included three categories: 1) non-arthritic control group, including women answering "no" to the initial arthritis question; 2) OA group, including those women answering "yes" to the initial arthritis question and answering "other/do not know" on the arthritis type question; and 3) probable RA group, those women reporting RA plus one of the commonly used rheumatology DMARDs or glucocorticoids. Women were excluded if they did not respond to the initial or follow-up arthritis question, if they reported RA but did not report one of the treatment medications of interest, or if they reported other rheumatologic or inflammatory arthritic conditions including lupus or ulcerative colitis.

Fracture Ascertainment

The participants self-reported clinical fractures during medical updates that occurred every six months for women participating in the clinical trials (CT), and yearly for the women participating in the observational study (OS). The WHI collected information on fracture types including: upper and lower arm, elbow, spine, tailbone, hip, upper and lower leg, and foot, but excluded fractures of the ribs, sternum, skull or face. All fractures reported in the CT and all hip fracture (CT and OS) were adjudicated by

review of radiologic reports or medical records by centrally trained and masked physicians (101). The fractures of interest in this analysis included total (any type of fracture), spine, and hip.

Covariates

Variables associated with arthritis and/or fractures were considered as possible covariates including; age, race/ethnicity, height, weight, education, income, physical activity, hospitalizations, number of falls in the previous year, smoking status, alcohol use, hormone use status, parental fracture >40 years, calcium and vitamin D intake, depression score, years since menopause, personal fracture after 55 years, joint replacements, general health score, and use of certain medications (phenobarbital, anticonvulsants, antiparkonsin drugs, antidepressants, anti-anxiety drugs, thyroid medicatoions, thiazolidinediones, proton pump inhibitors, thiazide diruetics, statins, bisphosponates, calcitonins, NSAIDS, estrogens, heparin, and selective-estrogen receptor modulators).

All covariates were assessed at baseline. Height and weight were measured using standardized procedures by WHI clinical staff. Race/ethnicity was classified into 6 categories: American Indian or Alaskan Native, Asian or Pacific Islander, African American, Hispanic/Latino, White (not of Hispanic origin), or other. Women reported highest level of education; if they had been hospitalized in the last 2 year (yes or no); if they had a fracture at the age of 55 or older (yes or no); and the number of times they fell to the ground in the past 12 months (0, 1, 2, 3 or greater). Summary variables on parental

fractures (yes or no), physical activity (metabolic equivalence units (METs) per week), hormone use (never, past, or current user), smoking (non, past, or current smoker) and alcohol use (non, past, or current drinker) were generated based questionnaire responses. Years since menopause were calculated based on reported last menstrual period. Questions from the Rand 36-Item Health Survey (SF-36) were used to compute a general health construct, and questions from the center for epidemiological studies depression scale (CES-D) were used to calculate a depression score. Dietary calcium and vitamin D amounts generated from food frequency questionnaire data were combined with amounts reported from supplemental use to generate total calcium and vitamin D variables. Binary (yes/no) variables for each class of drugs were used, and bisphosphonates and calcitonin were combined to create an osteoporosis medication summary variable. Variables related to the WHI design, such as clinical trial assignment (not randomized, placebo, or intervention), were also included as covariates.

Statistical Analysis

Descriptive statistics by arthritis group were compared using analysis of variance (ANOVA) for continuous variables and chi-squared tests for categorical variables. Age-adjusted fractures rates were calculated using direct standardization. Cox-proportional hazards models were used to estimate risk of fracture between the arthritis groups. Days from randomization to fracture served as the event time, and days from randomization to last contact served as the censoring time for those who did not fracture. Marginal analyses were performed for each covariate, and the variable was included in the full

model if significant $p<0.2$. Backwards elimination model building techniques were used to produce the final model, including all variables statistically ($p<0.05$) or biologically meaningful. Survival estimates were generated to graphically portray group differences in fracture risk over time. Ethnicity and glucocorticoid (GC) interactions were tested using cross-product interaction terms (for example arthritis*ethnicity) and/or stratified analyses. All analyses were performed in Stata vs. 10 (Statacorp, College Station, TX).

RESULTS

Of the 161,808 women enrolled in the WHI, 147,657 were not missing arthritis information and did not report other inflammatory and/or rheumatologic conditions, such as lupus or ulcerative colitis. Of that, 83,295 (56.4%) were included in the non-arthritic control group. Of the women who reported arthritis, 63,402(42.9%) were placed in the OA group, and 960 (0.7%) women met the criteria for the probable RA group. All other women were excluded from analyses.

Significant differences in demographic and lifestyle variables by arthritis group were present. The OA and RA groups were slightly older than the control group (2.89 years on average), and the arthritis groups had a larger percentage of African Americans with 13.2% of the RA populations being African American, compared to 9.3% in the OA group and 8.2% in the control group. The OA group had the largest mean weight (75.4 kg) followed by the RA group (73.2kg) and the non-arthritic control group (71.7 kg).

The rate of parental fracture, smoking status, and hormone therapy use were similar between the three groups. The RA group had a larger percentage of

hospitalization the last 2 years (28.0% vs. 18.4% and 11.6%), and history of fracture at age 55 years or greater (19.9%) than the other two groups (18.8% and 14.1%). Complete descriptive information can be found in Table 11.

Fractures in the WHI

As of March 2008, the women were followed for a mean of 7.83 years, and 24,137 clinical fractures of any type, 2,559 fractures of the spine, and 1,698 hip fractures were reported in the study population (Table 12). The age-adjusted rate (95% confidence interval) per 10,000 women years for sustaining a fracture of any type was 211.4 (207.6, 215.1) in the control group, increasing to 250.6 (245.8, 255.3) in the OA group, and 364.2 (317.1, 411.3) in the RA group (Figure 2). The age-adjusted spine fracture rate increased by 1.4 fold between the control group and the OA group, and increased again by 1.9-fold between the OA and RA group. There was no difference in hip fracture rates between the control group and the OA group (13.9/10,000 vs 15.7/10,000), but there was an increase in the hip fracture rate in the RA group (50.7/10,000) (Figure 2).

The Association between Arthritis and Fracture Risk

Covariates included in the final Cox-proportional hazards model included: age, race/ethnicity, height, weight, physical activity, assignment in all clinical trials, hospitalizations, number of falls, smoking status, hormone use, parental fracture >age 40, total calcium and vitamin D intake, depression score, years since menopause, diabetic treatments, osteoporosis medication, general health score, personal fracture >55, and joint

replacements. In comparison to the non-arthritic control group, the hazard ratio (95% CI) for any fracture in the OA group was 1.09 (1.05, 1.13) and 1.49 (1.27, 1.76) in the RA group (Table 13). Similarly, the OA group had a 16% increase ($p<0.05$) and the RA group had a 2-fold increase in fractures of the spine compared to the non-arthritic control group (Table 13). The risk of hip fractures was 3-fold in the RA group compared to the non-arthritic control group (3.08 (2.07, 4.59)), whereas the OA group had a non-statistically significant increase (1.11 (0.98, 1.25)) in hip fracture risk compared to the control group (Table 13). Survival curves by arthritis group for all clinical fractures are plotted in figure 3.

Testing Age, Ethnicity, and Glucocorticoid Interactions

The race and ethnic distribution of fractures was calculated for each fracture type to examine if ethnicity modified the effect between arthritis and fracture. The majority of women sustaining any type of fracture in the non-arthritic control group were non-Hispanic white (89%). African American and Hispanic women made up 5% and 2.5% of the total fracture cases in the non-arthritic group. The ethnic distribution of total fractures (all fractures combined) was similar in women with OA compared to women without arthritis. However, the total fracture race and ethnicity distribution was different between the RA group and the non-arthritis group, with 9.7% of the African American women in the RA reporting a fracture compared to only 5% of the African American women in the non-arthritic and OA groups. The higher percentage of African Americans reporting a fracture in the probable RA group compared to the other two groups was also

seen in spine and hip fracture (Table 14). Though differences were seen in fracture frequency by ethnicity, neither the Cox-model hazards ratios using the interaction term (arthritis*ethnicity) nor the Mantel-Haenzel stratified odds ratios were statistically significant.

A glucocorticoid (GC) use cross product interaction term (GC*Arthritis) could not be utilized in Cox models since GCs were used as one of the agents to validate RA. To assess the influence of GC use, two additional models were performed. The first included an arthritis variable where GCs were not used in RA definition, which allowed for formal interaction testing (GC*arthritis) to be performed, as well as adjustment for GC use in the. The second model involved a new arthritis and GC categorical variable.

The sample size of the probable RA group decreased from 960 to 790 as 170 of the women who self-reported RA only reported using GCs and no other DMARD. Fracture risk estimates changed slightly with the smaller sample size and the inclusion of GC's as a covariate; however, the OA and probable RA risk estimates for any fracture and hip fracture were similar to the results including GCs as a RA validation medication (Table 15). Major hazard ratio changes were observed in risk for spine fracture in the RA group when adjusting for GC use, with a decrease in the hazard ratio from 1.93 (1.29, 2.90) in the initial analysis (Table 13) to 1.54 (0.93, 2.53) when adjusting for GC use (Table 15).

The new arthritis and GC use categorical variables included the following categories: $Arthritis^{--}GC^{--}$, $Arthritis^{--}GC^{++}$, $OA^{++}GC^{--}$, $OA^{++}GC^{++}$, $RA^{++}GC^{--}$, $RA^{++}GC^{++}$. GC use increased the risk of fracture compared to non-users. For example, when

compared to those women without arthritis and not using GCs, the GC users in the OA group had a significant 34% increase risk for sustaining any type of fracture, where as the OA non-GC users had a significant 9% increase risk in any fracture (Table 16). Similar results were seen in spine and hip fractures, and the effect of GC use was most prominent in the RA group than the other arthritis categories. However, the hazard ratios found for the GC^{++} and GC^{-}categories in each arthritis type overlapped, signifying no statistically significant modification of the risk of fracture in each of the arthritis types by GC use (Table 16), agreeing with the non-statistically significant GC*arthritis interaction term.

DISCUSSION

In this large population of postmenopausal women, self-reported arthritis is associated with significant fracture risk increase in women reporting OA and RA. Women in the probable RA group had a significant 50%, 2-fold, and 3-fold increase in total, spine, and hip fractures compared to the non-arthritis control group respectively; and women in the OA group had a significant 9% and 16% increase in total and spine fractures, and a marginally significant 11% increase in hip fractures compared to the non-arthritis control group.

The RA findings from this study are consistent with the literature showing an increased risk of fractures in RA patients (15, 16, 81). RA patients had an average 2-fold increase risk of proximal femur and pelvic fractures in a population based study by Hooyman and colleagues (15), and after adjusting for age and sex, hip fracture risk was nearly 3-fold higher in Finish RA patients compared to controls (16). Recently, incidence

of any, spine and hip fracture in the Consortium of Rheumatology Researchers of North American (CORRONA) Registry was reported to be 3.71, 0.78, and 0.66 per 100 person-years (112). The age-adjusted fracture rates for the probable RA group were 3.64, 0.49, and 0.50 per 100 person-years for total, spine, and hip fracture in the WHI, and though the CORRONA registry includes premenopausal women and men, the incidence rates of the nationwide CORRONA registry are comparable to the rates found in the WHI.

General lifestyle and demographic osteoporosis risk factors, such as age, smoking, and physical activity, play a significant role in fracture risk and have been considered as covariates in a variety of RA and fracture studies (113); however, the primary risk factor for fracture in RA and non RA populations is low BMD. It has been well documented that RA patients have lower BMD at many skeletal sites compared to various control populations (12, 13, 79), and though BMD was not examined in this study, it is highly probable that the associations seen in this study are driven in part by BMD. Associations between RA and hip structural geometry and body composition, two variables associated with bone strength and fracture risk, will be examined in subsequent chapters of this dissertation.

The risk of sustaining any clinical fracture and a spinal fracture was modestly but significantly increased by 13% in the OA group compared to the non-arthritic controls. It is likely that the effects of OA on fracture rate are being underestimated in this study due to misclassification errors inherent in self-reporting OA. As previously mentioned, the reporting of an association between OA and fracture has been mixed in the literature. The most recent study to suggest OA increases the risk of fractures found that after adjusting

for falls and the use of walking aids, the risk for nonvertebral fractures significantly increased by 48% in their clinician diagnosed knee OA patients, and though not significant, the risk for hip fractures increased by 84% (111). Though our study is in agreement with the Arden study, the use of clinically diagnosed, site-specific OA patients yielded higher fracture estimates than those found in this study using self-reported OA cases.

The most recent study showing a protective effect of OA on fracture risk was a case-control population-based study conducted in Denmark, which after adjustment for several variables, found an average fracture risk reduction of 23% and 16% for OA of the hip and knee, respectively (114). Population demographics could be the primary explanation for the difference associations seen between the Vestergaard study and ours, as the Danish population used was almost 20 years younger than the WHI population.

Though a consensus has not been reached, several biological mechanisms have been proposed relating OA to fracture. Like RA, the increase in fracture in OA patients could be driven through a BMD pathway. Studies have shown BMD in OA populations are typically higher than non-arthritic populations (115-117), therefore, this argument does not provide a good explanation for increases in fracture. When stratified by BMD, Bergink and colleagues found significant increases in nonvertebral and wrist fractures in the OA group with a high BMD, whereas no significant increase was seen in OA patients with a low BMD (110). There have also been longitudinal studies suggesting OA patients have an increased rate of bone loss compared to controls (11, 115). While our study did not concentrate on measures of bone strength, our data is supportive of the

possibility that bone strength alterations in OA patients contributes to increased fracture rates.

Obesity has been shown to alter both the material and structural properties of bone strength. Travison and colleagues reported that lean mass and not fat mass, is association with various indices of femur strength, as estimated from hip structural analysis of DXA scans; suggesting that fat mass does not benefit the strength of the hip (50). Similarly Beck and colleagues reported that after adjusting for body weight, femoral BMD and other structural geometry indices decreased as body mass index (BMI) increased (51). Structural geometry has also been assessed in a group of OA patients, and results show that alterations in geometry precede OA diagnosis (118), again suggesting some biological process involved in OA alters the strength of bones. Based on these studies, obesity, a very prevalent condition in OA, could be one of the processes responsible for altering bone strength and increasing fracture risk in OA.

Falling, is another proposed OA fracture mechanism, as OA, especially at sites like the knee and hip, is associated with increased pain, and decreased postural stability and muscle strength, all which have been shown to be significant contributors to fall risk (119-121). Falling is a well-documented risk factor for fractures (1), and early studies have shown that the self-report of OA is associated with increased risk of falls (122, 123). More recently, Foley and colleagues did not see increased risk for falls in knee and hip radiographic OA cases, but did see that report of pain is highly associated with falls and OA patients reported more pain (124).

One last possibility is that the results represent the consequences related to behavioral and physiologic changes that occur in individuals that perceive articular discomfort they classify as arthritis. Self-reported health status has been shown to be an independent risk factor for fractures in many studies (125-129). It is possible that self-reported arthritis in the WHI is a measure of autoperception that encompasses a variety of health domains, such as pain, balance confidence, self-efficacy, and functional status.

Strengths and Limitations

This study has several limitations related to the arthritis exposure. The limitations of validity of self-report and the use of a proxy measure of OA within the WHI previously described by Wright and colleagues apply to this analysis (130). Though not clinically diagnosed, people experiencing joint pain due to a previous injury or conditions such as tendonitis, may report having OA. This can lead to a moderate amount of misclassification, biasing the estimates towards the null or making it less likely to show an effect.

Fracture risk is probably different for persons with OA of the hip compared to persons with knee, hand, or spine OA. The OA affected area may have artifactually higher BMD, whereas regions without OA have normal or low BMD, potentially altering overall fracture risk. By not having site specific or radiographically confirmed OA cases, the results are again potentially biased. Though Wright and colleagues previously published that the other/do not know group serves as the proxy for OA (130), Walitt et al found that using a similar medication use validation methodology, self-reported OA in

the WHI was very sensitive (95.0%), not particularly specific (23.4%), and only had fair agreement between self-reported OA and chart review (kappa = 0.23) (unpublished data).

Walitt and colleagues found that the combination of self-report and medication had the highest positive predictive value (62.2%) for RA (100), which potentially captured the "true" RA cases. However, these may represent the more severe cases, which could potentially overestimate the affect of RA on fracture risk. This study did not take into account incident cases of arthritis and the effect it has on fracture risk, and it did not account for the additive or multiplicative effect of having both OA and RA on fracture risk.

The use of self-reported fracture outcomes can also be seen as a limitation; however, sensitivity analyses were performed on adjudicated fractures only, and though slight changes in the point estimates were observed with the smaller sample size, the overall conclusions did not change. Chen and colleagues found high agreement between self-report and adjudicated fractures in WHI sub-study (131), assuring high quality of the fracture data used in this study.

Though GCs have known effects on calcium absorption and bone remodeling (132, 133) and have been shown to be associated with an increased risk for fractures (134), it is not clear whether GCs affect the risk of fracture directly or if the patients prescribed GCs are more likely to have advanced disease or be functionally limited, which increases their fracture risk (84). Studies show that RA patients using GCs have an increased risk of vertebral hip fractures, with one study showing a 42% increase risk in vertebral (82) and another showing 2.8-fold increase in hip fractures (83). Initially, GCs

were not included as a covariate in this study because they were used in the RA definition, but in after redefining the RA group without GCs and controlling for use, results showed that RA was no longer significantly associated with increased risk for spine fractures, and though significant, the magnitude of risk for any and hip fractures reduced slightly. These results are based on a smaller sample size (790 vs. 960); however, the only major difference found in demographics between the RA group with DMARD and GC in the definition and the RA group with only DMARDs in the definition was age. The GC definition group was on average 2 years older than the DMARD only definition group. As age was adjusted for in the models, these differences in demographics would not explain the findings alone.

In testing if glucocorticoids use modified the association between arthritis and fracture, a new categorical variable capturing users and non-users in each arthritis group was created. Though not statistically significant interaction was present, the fracture risk was higher in GC users compared to non-users, particularly in spine and hip fractures. In the RA group, GC use significantly increased the risk of spine fractures 2.5-fold compared to the non-arthritis/non-GC group, whereas RA alone without GC use was not statistically significant between the non-arthritis/non-GC reference group. GCs have a high predilection for decreasing vertebral bone mass (135), which explain why the effect of GC use was evident in spine fracture compared to the other fracture types.

Though limited by the above mentioned factors, there are many strengths of the study. The most notable is the size of the WHI, and the size of each of the exposure groups. Having over 63,000 women in the OA and over 900 in the RA group gave more

than adequate power to estimate the effects of arthritis on fracture outcomes. Most of the OA and RA limitations presented would have resulted in estimates being biased toward the null; however, significant association remained in our study. Though not clinically ascertained, the prevalence of OA in the WHI population was approximately 43%, which is comparable to the 42% prevalence of radiographic OA in the hands, knees, and hips found in the women 60 years and older participating in NHANES III (104). The WHI also had a larger percentage of women from minority groups, which allowed for examination of effect modification by race or ethnicity. The women of the WHI were followed on average almost 8 years, ensuring adequate numbers of fracture outcomes, especially for the more rare hip fracture outcome.

CONCLUSIONS

Arthritis and osteoporosis are important public health conditions for older adults. OA and RA affect over 25 million adults and fractures costs billions of health care dollars annually. The increase in fracture risk found in this study confirms the importance of fracture prevention in both patients with RA and OA.

Table 11: Baseline Characteristics by Arthritis Status

	No Arthritis* (n=83,295)		OA* (n=63,402)		RA* (n=960)	
	N	%	N	%	N	%
Baseline Age Group						
50-59	33,804	40.58	15,378	24.25	240	25.00
60-69	35,446	42.55	30,248	47.71	448	46.67
70-79	14,045	16.86	17,776	28.04	272	28.33
Race/Ethnicity						
White	68,699	82.68	53,153	84.05	741	77.35
Hispanic	3,573	4.30	2,060	3.26	38	3.97
African American	6,817	8.20	5,857	9.26	126	13.15
Asian	2,721	3.28	1,191	1.88	26	2.71
American Indian	317	0.38	292	0.46	9	0.94
Unknown	967	1.16	686	1.09	18	1.88
Hormone Trial						
Not randomized	68,819	82.62	53,487	84.36	878	91.46
Intervention	7,374	8.85	4,887	7.71	41	4.27
Control	7,102	8.53	5,028	7.93	41	4.27
Dietary Modification Trial						
Not randomized	57,310	68.80	45,779	72.20	812	84.58
Intervention	10,398	12.48	7,069	11.15	59	6.15
Control	15,587	18.71	10,554	16.65	89	9.27
Calcium and Vitamin D Trial						
Not randomized	63,522	76.26	50,503	79.66	866	90.21
Intervention	9,906	11.89	6,434	10.15	53	5.52
Control	9,867	11.85	6,465	10.20	41	4.27
Hospitalized in Last 2 Years						
No	69,909	88.43	51,453	81.59	683	72.05

Yes	9,143	11.57	11,607	18.41	265	27.95
Number of Falls in 12 Months						
0	57,007	71.34	40,530	64.10	612	64.15
1	15,054	18.84	13,331	21.08	201	21.07
2	5,454	6.83	6,123	9.68	97	10.17
3+	2,398	3.00	3,248	5.14	44	4.61
Parental Fracture >40 Years						
No	47,303	61.00	34,447	59.34	547	62.37
Yes	30,242	39.00	23,605	40.66	330	37.63
Fracture at Age 55+						
No	52,476	85.93	43,140	81.24	631	80.08
Yes	8,595	14.07	9,961	18.76	157	19.92
Smoking Status						
Never smoked	42,597	51.69	31,502	50.34	437	46.00
Past smoker	33,770	40.98	27,124	43.35	443	46.63
Current smoker	6,046	7.34	3,947	6.31	70	7.37
Hormone Therapy Use						
Never used	37,413	44.95	26,774	42.27	397	41.40
Past user	12,221	14.68	10,979	17.33	161	16.79
Current user	33,593	40.36	25,589	40.40	401	41.81
Osteoporosis Medications Use						
No	81,787	98.19	61,653	97.24	892	92.92
Yes	1,508	1.81	1,749	2.76	68	7.08
Thiazolidinediones Use						
No	83,240	99.93	63,339	99.90	958	99.79
Yes	55	0.07	63	0.10	2	0.21
Previous Joint Replacement						
No	77,918	99.20	58,604	93.29	773	81.28
Yes	628	0.80	4,218	6.71	178	18.72

	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**

Age (yrs)	61.89	7.14	64.81	7.01	64.75	7.12
Height (cm)	162.00	6.58	161.50	6.73	161.10	6.76
Weight (kg)	71.74	15.94	75.45	17.71	73.18	17.78
Years Since Menopause	13.60	9.36	16.90	9.62	16.71	9.97
Total Calcium Intake (mg)	1,148.00	750.00	1,207	734.10	1,264.00	837.60
Total Vitamin D Intake (mg)	8.92	6.87	9.66	7.12	9.88	6.84
CES-D Depression Score	0.03	0.11	0.05	0.14	0.05	0.14
Total Physical Activity per Week (METS)	13.35	14.34	11.53	12.92	9.58	11.46
General Health Construct	78.52	16.00	70.03	18.07	57.26	20.35

OA: Osteoarthritis
RA: Rheumatoid arthritis

*all variables significantly different between the three groups at $p<0.001$, with the exception of thiazolidinediones ($p=0.020$)

Table 12: Frequency of Fracture in the WHI and by Arthritis Status

	No Arthritis (n = 83,295)		OA (n = 63,402)		RA (n = 960)			Total Population (n = 147,657)	
	N	%	N	%	N	%	p-value	N	%
Any Fracture	12,411	14.9	11,488	18.1	238	24.8	<0.001	24,137	16.3
Spine	1,126	1.4	1,395	2.2	38	4.0	<0.001	2,559	1.7
Hip	775	0.9	885	1.4	38	4.0	<0.001	1,698	1.1

Table 13: The Risk of Fracture by Arthritis Group

	No Arthritis (n=83,295)	**OA (n=63,402)**	**RA (n=960)**
Any Fracture (n=24,137)	Ref.	1.09 (1.05, 1.13)	1.49 (1.27, 1.76)
Spine (n=2,559)	Ref.	1.16 (1.05, 1.29)	1.93 (1.29, 2.90)
Hip (n=1,698)	Ref.	1.11 (0.98, 1.25)	3.08 (2.07, 4.59)

* Adjusted for age; race; height; weight; physical activity; assignment in the HT trial, DM trial, and CaD trial; hospitalizations; falls; smoking ; hormone use; parental fracture >age 40; calcium & vitamin D intake; depression score; years since menopause; diabetic treatments; osteoporosis medication; general health score; fracture >55; and joint replacements

Table 14. Frequency of Fracture by Arthritis Status and Race/Ethnicity

Any Fracture (n=24,137)			
	No Arthritis (n=12,411) Mean (%)	**OA (n=11,488) Mean (%)**	**RA (n=238) Mean (%)**
Non-Hispanic White	11,015 (88.8)	10,268 (89.4)	195 (81.9)
Hispanic White	314 (2.5)	264 (2.3)	7 (2.9)
African American	621 (5.0)	616 (5.4)	23 (9.7)
Asian/Pacific Islander	273 (2.2)	143 (1.2)	4 (1.7)
American Indian/Alaskan Native	48 (0.4)	53 (0.5)	5 (2.1)
Spine Fracture (n=2,559)			
	No Arthritis (n=1,126) Mean (%)	**OA (n=1,395) Mean (%)**	**RA (n=38) Mean (%)**
Non-Hispanic White	1,046 (92.9)	1,307 (93.7)	35 (92.1)
Hispanic White	19 (1.7)	19 (1.4)	1 (2.6)
African American	17 (1.5)	19 (1.4)	2 (5.3)
Asian/Pacific Islander	26 (2.3)	20 (1.4)	0 (0.0)
American Indian/Alaskan Native	2 (0.2)	8 (0.6)	0 (0.0)
Hip Fracture (n=1,698)			
	No Arthritis (n=775) Mean (%)	**OA (n=885) Mean (%)**	**RA (n=38) Mean (%)**
Non-Hispanic White	726 (94.0)	837 (94.8)	32 (84.2)
Hispanic White	11 (1.4)	9 (1.0)	1 (2.6)
African American	19 (2.5)	21 (2.4)	3 (7.9)
Asian/Pacific Islander	8 (1.0)	7 (0.8)	2 (5.3)
American Indian/Alaskan Native	2 (0.3)	5 (0.6)	0 (0.0)

Table 15. Risk of Fracture by Arthritis Status With Glucocorticoids Not Used in RA Definition

	No Arthritis (n=83,295)	**OA (n=63,402)**	**RA (n=790)**
Any Fracture (n=24,098)	Ref.	1.09 (1.05, 1.13)	1.42 (1.18, 1.71)
Spine (n=2,550)	Ref.	1.16 (1.05, 1.29)	1.54 (0.93, 2.53)
Hip (n=1,691)	Ref.	1.10 (0.98, 1.25)	2.93 (1.86, 4.61)

***** Adjusted for age; race; height; weight; physical activity; assignment in the HT trial, DM trial, and CaD trial; hospitalizations; falls; smoking ; hormone use; parental fracture >age 40; calcium & vitamin D intake; depression score; years since menopause; diabetic treatments; osteoporosis medication; general health score; fracture >55; joint replacements; and glucocorticoid use

Table 16: Risk of Fracture by Arthritis and Glucocorticoid Use

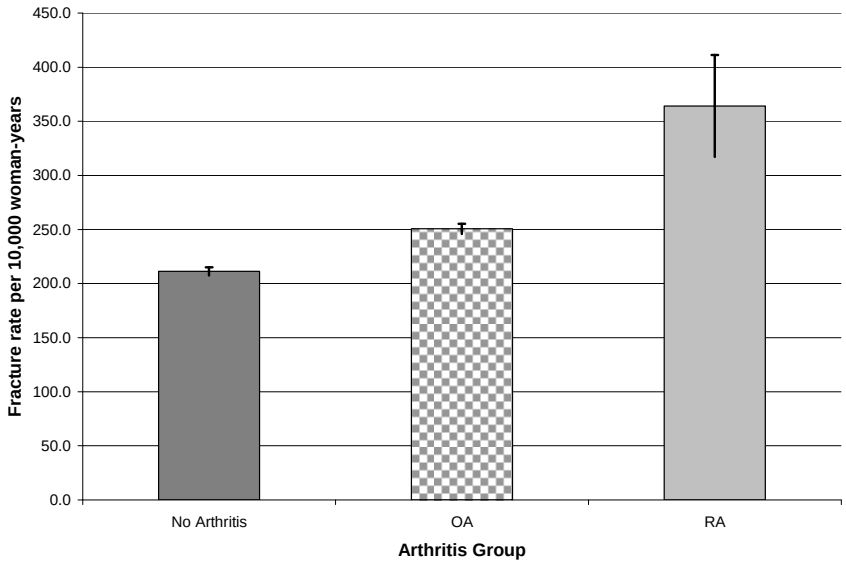
	Any Fracture HR (95% CI)	Spine HR (95% CI)	Hip HR (95% CI)
Arthritis^{--} GC^{--} (n = 82,947)	Ref.	Ref.	Ref.
Arthritis^{--} GC^{++} (n = 348)	1.16 (0.85, 1.58)	1.12 (0.46, 2.71)	1.34 (0.50, 3.61)
OA^{++} GC^{--} (n = 62,917)	1.09 (1.05, 1.13)	1.16 (1.05, 1.29)	1.11 (0.98, 1.25)
OA^{++} GC^{++} (n = 485)	1.34 (1.08, 1.67)	1.83 (1.13, 2.99)	1.79 (0.97, 3.28)
RA^{++} GC^{--} (n = 576)	1.48 (1.20, 1.83)	1.57 (0.88, 2.79)	2.91 (1.73, 4.91)
RA^{++} GC^{++} (n = 384)	1.52 (1.17, 1.96)	2.51 (1.44, 4.37)	3.41 (1.91, 6.10)

All models adjusted for age; race; height; weight; physical activity; assignment in the HT trial, DM trial, and CaD trial; hospitalizations; falls; smoking ; hormone use; parental fracture >age 40; calcium & vitamin D intake; depression score; years since menopause; diabetic treatments; osteoporosis medication; general health score; and fracture >55

GC = glucocorticoid
OA = osteoarthritis
RA = rheumatoid arthritis

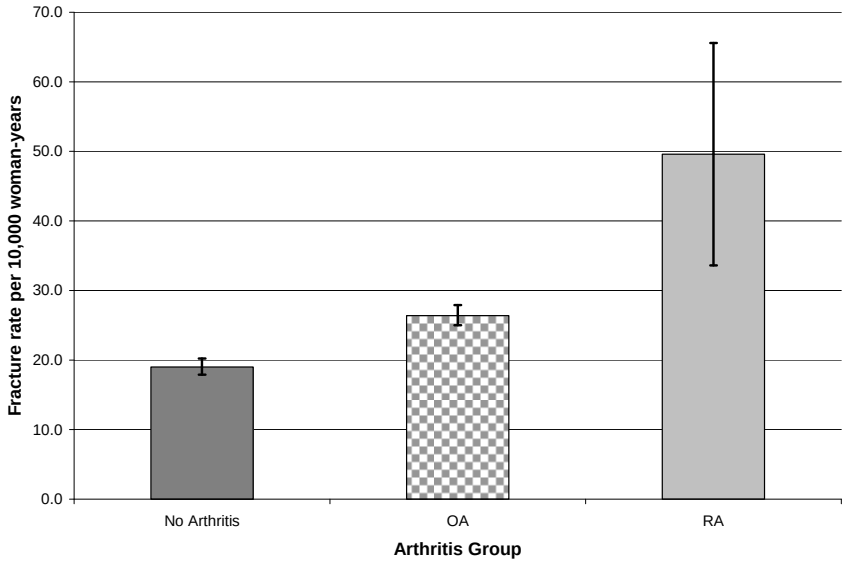
Figure 2: Age-Adjusted Fracture Rates by Arthritis Status

A) Total Fractures



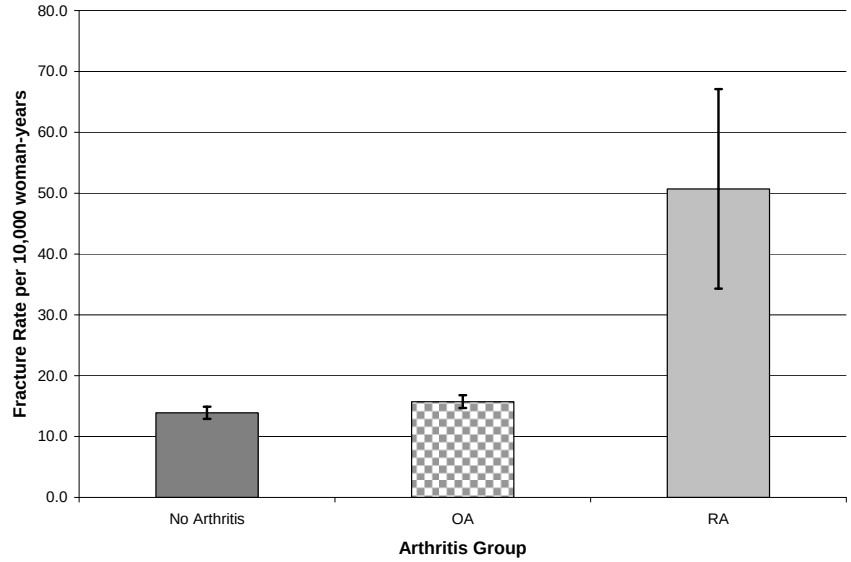
No Arthritis	OA	RA
211.4	250.6	364.2
(207.6, 215.1)	(245.8, 255.3)	(317.1, 411.3)

B) Spine Fractures



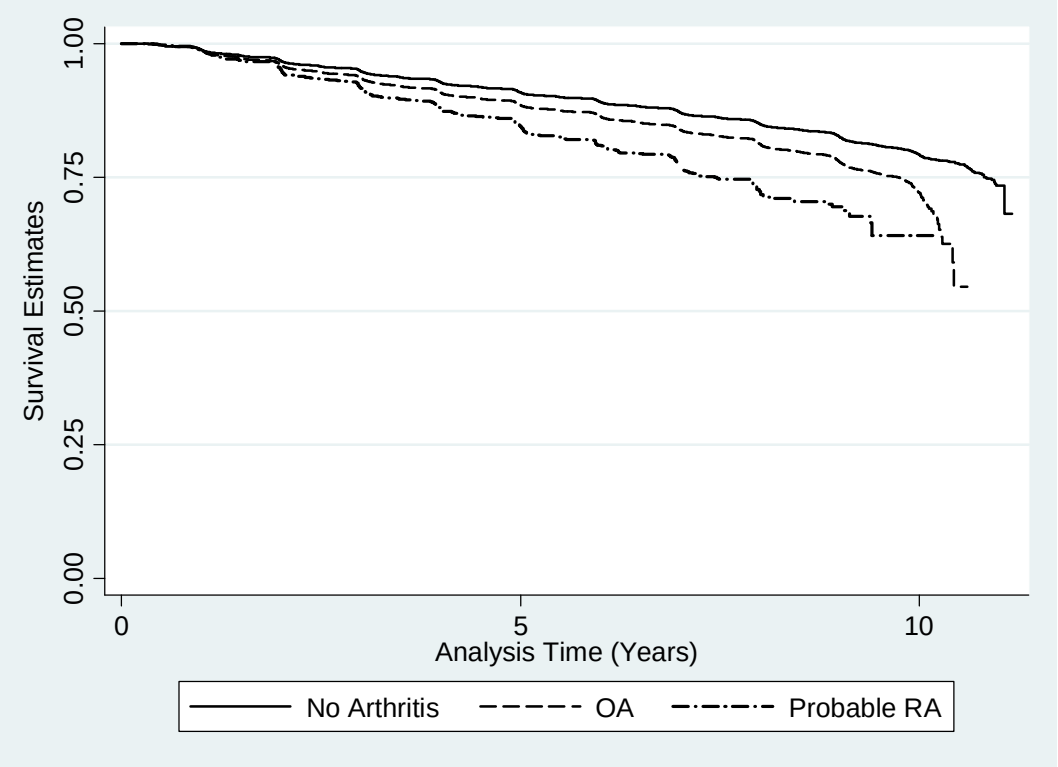
No Arthritis	OA	RA
19.0	26.4	49.6
(17.9, 20.2)	(25.0, 27.9)	(33.6, 65.6)

C) Hip Fractures



No Arthritis	OA	RA
13.9	15.7	50.7
(12.9, 14.9)	(14.7, 16.8)	(34.3, 67.1)

Figure 3: Survival Curve for Total Fractures by Arthritis Group



Log-Rank Test for equality of survivor functions $p<0.001$

OA: Osteoarthritis
RA: Rheumatoid Arthritis

CHAPTER 8: THE ASSOCIATION BETWEEN RHEUMATOID ARTHRITIS AND HIP STRUCTURAL GEOMETRY

INTRODUCTION

The previous study (chapter 7) showed that within the WHI, women with probable RA had a significant increase risk for fracture, especially hip fracture. The increased fractures risk association was irrespective of race or ethnicity, and though no statistically significant difference in users versus non-users for any or hip fracture, glucocorticoid use altered the association between RA and spine fracture risk. The mechanism of fracture in RA populations has been under investigation for several years, and as previously stated, low BMD is thought to be the primary factor in the increased fracture risk seen in RA patients. Significant decreases in BMD are correlated with increases in fracture risk (136-139), and RA patients have lower BMD than non-arthritic comparison populations (12, 13, 80).

As reported by Griffith, osteoporotic fractures occur "when bone strength is less than forces applied to the bone" (31), and as discussed in earlier sections, bone strength is comprised of both the material properties and structural properties, including architecture and geometry (33). The hip structural analysis (HSA) program developed by Beck and colleagues utilizes dual energy X-ray absorptiometry (DXA) images to extract limited structural parameters. Again, this is particularly advantageous to clinical and research practice as DXA is the method routinely used in the assessment of BMD. The HSA program has been used in a variety of studies, and significant improvements in hip

structure have been observed with the use of several therapeutic agents (35, 36, 38, 41, 140, 141).

To date, there have been no hip structure studies in RA populations. It is possible that the risk factors associated with low BMD in RA also have a negative impact on structural geometry, which could further increase the risk for fracture in this population. This epidemiologic investigation assessing the structural dynamics of bone over time may provide information on the role of hip structure in fracture risk. The objectives of this section of the study are to: 1) assess the longitudinal changes in bone strength in RA compared to non-arthritic controls, and 2) test if age, ethnicity, time, or glucocorticoid use alters the association between RA and bone strength loss in a population of postmenopausal women from the Women's Health Initiative.

METHODS

Study Population

This study was performed in participants of the Women's Health Initiative Bone Mineral Density (WHI-BMD) centers, which is comprised of the clinical centers at Tucson/Phoenix, AZ; Birmingham, AL; and Pittsburgh, PA. Women enrolled in these centers (n=11,020) had DXA scans on a Hologic QDR 2000 or 4500W machine (Hologic; Waltham MA) to measure bone density at the spine, areal hip, and total body; in addition to whole body and regional body composition. The scans were completed at baseline, years 3, 6, and 9 for participants of the OS; and baseline, years 1, 3, 6, 9, and closeout of the study for CT participants.

Three arthritis groups will be used in this analysis: 1) probable RA, defined using the methodology previously described on p.49; 2) self-reported RA, those women self-reporting RA, but did not report one of the specific medications; and 3) non-arthritic controls, or those women who did not report arthritis in the baseline assessment. Though the previous analysis found an increase risk for fracture in the OA group, it was decided not to use the OA group as a comparison population in this study because of the large potential for misclassification. The self-reported RA group was included as a comparison population to begin to address the demographic and lifestyle characteristic differences between the probable and self-reported groups.

Ascertainment of Hip Strength using Hip Structural Analysis

The structural geometry of the proximal femur was ascertained by applying the HSA program to archived DXA (baseline, years, 3, 6, and 9) scans to produce estimates of bone strength at three femur cross-sections; the narrow neck (NN), intertrochanteric (IT), and shaft (S). Details on the specifics of HSA have been previously published (34) and are described on pages 28-29, but in summary, the HSA program computes at each of the 3 cross-sections: conventional BMD, bone cross-sectional area (CSA), bone outer diameter (OD), and the center of mass of each cross-section; in addition to measuring femur neck length, neck-shaft angle, and cortical thickness at each cross-section. Center of mass and cortical thickness are used to calculate section modulus (SM) and buckling ratio (BR). Section modulus is an index of bending strength of the cross-section, and

buckling ratio is an index of susceptibility to local cortical buckling under compressive loads.

DXA Quality Control

The WHI center at the University of California, San Francisco (UCSF Prevention Sciences, San Francisco, CA) served as the BMD quality control center, which included monitoring DXA operator performance, DXA machine performance, and managing DXA databases from the three WHI clinic centers. Three Hologic spine, hip, and linearity phantoms were exchanged among the centers to assess quality control and cross-calibration. For the structural measurements, a separate cross-calibration was conducted using a special phantom designed for the HSA method. Sensitivity of HSA was not examined in this study, however, previous studies using the program have found moderate to good reliability with coefficient of variations ranging from 0.8% to 7.2% (142, 143).

Covariates

Variables potentially related to RA, BMD or to bone strength were assessed as potential covariates. These variables included: age, ethnicity, height, weight, body mass index (BMI), total body percent lean mass, smoking status, hormone use status, physical activity, dietary energy, total calcium intake, total vitamin D intake, use of certain medications (thiazide diuretic, statins, anti-convulsants, thyroid drugs, proton pump inhibitors, bisphosphonates, calcitonin, parathyroid hormone, non steroidal anti-

inflammatory drugs, estrogens, phenobarbital, and heparin), and variables relevant to the WHI (clinical center, participation in HT or CaD trial). Covariates were assessed at baseline using either questionnaire data (age, ethnicity, smoking, hormone use, physical activity, nutritional factors, and medications), or physical measurements (height, weight, BMI), or DXA derived estimates (percent lean mass).

Statistical Analysis

Descriptive variables reported by the three groups at baseline (No arthritis, self-reported RA, probable RA) were compared using analysis of variance (ANOVA) for continuous variables or chi-squared test for categorical variables. The association between RA and hip strength was tested using both cross-sectional and longitudinal analyses. For the cross-sectional analysis mean hip strength parameters were compared at each time point between the three groups using ANOVA. Linear mixed effects models (LMM), which incorporate all time observations (baseline, year 3, 6, and 9) in one model, were used to analyze the association between RA and hip strength longitudinally. The random coefficient model (RCM) was used to control for serial correlation in the longitudinal data by fitting a slope and intercept within each subjects hip strength measure, which were included as random effects in the LMM. The base model included the hip strength parameter as the dependent variable, RA status and the baseline hip strength parameter as the independent variables. Marginal analyses were performed independently with each covariate and those with a p-value <0.20 were tested in the full model. Backwards elimination techniques were then used to generate the final model,

which included all variables $p<0.05$ and other variables deemed clinically or biologically important. The interaction between age, ethnicity, time, and glucocorticoid use, and the associations between RA and hip structure were tested. All analyses were performed in STATA v.10 (College Station, TX).

RESULTS

A total of 11,020 women were enrolled in the WHI-BMD cohort. The baseline health assessment questionnaire was completed by 10,858 participants of which, 5,253 women reported not having arthritis, and 5,605 responding yes to the initial arthritis question. Of the self-reported arthritis patients, 584 self-reported RA and 4,348 reported other types of arthritis. After reviewing baseline medication, 83 (14.2%) of the self-reported RA cases also reported at least one of the commonly used anti-rheumatic agents. Baseline hip structural geometry measurements were available for 4,779 of the non-arthritic controls, 453 of the self-reported RA cases, and 78 of the probable RA cases. Sample size at each study visit and the number of observations used in modeling can be found in Table 17.

Baseline Characteristics

Significant differences between the three groups were seen in several baseline demographic variables. Both the self-reported and probable RA groups were significantly older than the non-arthritic control group with mean (SD) values of 65.4 (7.5), 64.6 (7.7), and 61.7 (7.4) years for the probable RA, self-reported RA and non-arthritic controls

respectively. The non-arthritic control group was slightly taller (0.92 cm on average) than the probable and self-reported RA cases, and the non-arthritic control group weighed less (4.8 kg less on average) than the RA groups. The self-reported RA cases had the highest body weight (77.0 kg), followed by the probable RA group (74.7 kg), then the non-arthritic control group (72.2 kg). Ethnicity also varied significantly ($p<0.001$) between the groups, with a higher percentage of African Americans in both the self-reported RA (20%) and the probable RA groups (28.6%) compared to the non-arthritic group (13.0%).

There were slight differences in lifestyle factors between groups. The probable RA group had a higher but non-significant percentage of women currently using postmenopausal hormone therapy (HT) (42.3% vs. 32.1% self-reported and 35.3% in the non-RA controls. There were no significant differences between reports of energy intake, energy expended through physical activity, and intake of vitamin D between groups. Physical function was significantly reduced by RA status ($p<0.001$). Non-arthritic controls had a mean (SD) physical function score of 85.9 (16.4), whereas the self-reported RA had a mean score of 69.6 (23.1), and the probable RA group had a mean score of 53.8 (25.0). Complete information on baseline demographics by RA status can be found in Table 18.

The Association between RA and Hip Structural Geometry

A decrease in hip BMD and strength was observed over the nine years of study in all groups (Table 19). After adjusting for age, the mean of hip BMD and the various

strength variables were smaller in the probable RA group compared to the non-arthritic control group at baseline and each year of study (Table 19). This trend was observed at all regions; however, the mean difference was greatest at the narrow neck. The differences between the probable RA and non-arthritic control groups were not statistically significant in the cross-sectional analysis. Examining the data longitudinally provided the opportunity to increase the analytical power by including all time points in one model in addition to controlling for all other important covariates not examined in the cross-sectional analysis.

The longitudinal association between RA and hip strength was adjusted for visit (time), baseline strength parameter, age, ethnicity, clinical center, height, weight, total body percent lean mass, randomization status in the CaD and HT trial (not randomized, intervention or placebo), hormone use, anticonvulsant and osteoporosis medication use in the final RCM. With inclusion of all time points in one model, significant decreases in strength were only seen in the probable RA group (Table 20 & Figure 4). The probable RA group had a statistically lower mean BMD, OD, CSA, and SM at a fixed rate over the study period at the narrow neck region. Though not statistically significant, the BR coefficient was higher (indicating decreased ability to resist local buckling) in the probable RA group. The magnitude of the association between RA and hip strength in the intertrochanter and the shaft region was not as large as at the narrow neck resulting in non-statistically significant effects, but similar decreasing trends in strength were seen in the probable RA group. Results from the random coefficient models for each region can

be found on table 20 and the longitudinal graphs for the predicted narrow neck region can be found in Figure 4.

Testing Age, Ethnicity, Time, and Glucocorticoid Interactions

No differential effect in hip strength was seen by baseline age or ethnicity, and there was no statistical difference in the rate of loss between three groups over time. To test the possible glucocorticoid (GC) interaction, a new categorical variable similar to the one used in chapter 7, was created to capture both RA status and GC use at baseline, and included the following categories: $RA^{-}GC^{--}$(n = 4,755), $RA^{-}GC^{++}$ (n = 24), $RA^{++}GC^{--}$ (n = 42), and $RA^{++}GC^{++}$ (n = 36). GCs were not reported in the self-reported RA cases, therefore they were not included in the subsequent analyses. In the cross-sectional analysis, GC use was associated with a general trend of decreasing BMD and hip strength without adjusting for covariates, with a smaller mean value in the hip strength parameters in the GC^{++} groups compared to their GC^{--} comparison group (Table 21). At the narrow neck region, the $RA^{++}GC^{++}$ group had the lowest mean BMD and hip strength measurement compared to the other groups; however, the difference in mean hip strength was not statistically significant between the groups at baseline (Table 21). Using the GC categorical variable in the full longitudinal models only showed a significant reduction in BMD and strength in $RA^{++}GC^{--}$ group, consistent with the main findings (Table 22).

DISCUSSION

This study confirmed the adverse effects of RA on hip BMD, and also showed that RA is associated with a decrease in structural integrity. Though small in number, the probable RA cases within the WHI-BMD centers had reduced BMD and structural geometry parameters in the narrow neck region at baseline, which decreased at a fixed rate throughout the nine years of study.

Significant positive effects of various treatments on hip structure at all regions have been shown. For example, Bonnick and colleagues recently reported a significant effect at all regions with once weekly aledronate and risendronate therapy, with the treatment effect being the strongest at the intertrochanteric region (37). Our study showed similar trends in decreased strength in the intertrochanteric and shaft regions; however, the magnitude of the association between RA and hip structure was smaller in magnitude and unlike the narrow neck region, did not reach statistical significance. Although systemic inflammation is a manifestation of RA, joints are the primary region affected by the disease. Of the regions analyzed, the narrow neck is closest to the hip joint, and synovial cytokines levels are folds higher than serum cytokine levels. In a study by Petrovic-Rackov and Pejnovic serum tumor necrosis factor-alpha (TNF-α) levels were 5.6±3.5 pg/ml, whereas synovial TNF-α levels were 14.0±19.4 pg/ml (144). The elevated inflammatory cytokines near the narrow neck region may make it more vulnerable to the erosive effects of the proliferative synovium of RA on bone mass and structure, possibly explaining the findings of our study.

Inflammation is the primary driver of deteriorating bone health in RA patients. Pro-inflammatory cytokines such as, interleukin (IL) – 1, IL-6, and TNF-α, have direct and indirect effects on osteoclasts, increasing bone resorption (72) and have been shown to be associated with markers of bone remodeling. In a study of Japanese RA patients, Momohara and colleagues found a positive correlation between inflammation and bone resorption markers (145). In contrast, Wislowska and colleagues did not find any correlation between measures of inflammation and bone resorption or bone resorption and BMD in a small group of RA patients (146). Though these studies were performed in different populations and had conflicting results, both used C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) as the laboratory marker of inflammation. Direct measurement of TNF-α, IL-1, IL-6, or other known inflammatory cytokine with adverse effects on osteoclasts, may have provided a significant negative correlation with bone mass. Though not exclusively studied, one can hypothesize that these inflammatory cytokines also negatively affect bone structure, providing molecular evidence for the declines in both bone quantity and quality in RA. Structural damage to the joint may also play a part, by changing the geometry and alignment of the hip.

Though GC use has adverse effects on bone health, our study did not show any modification on the RA and hip geometry association by GC use. In the non-RA population, GC use slightly reduced the mean BMD and strength estimates to that of the GC negative RA population, and further slightly reduced BMD and strength estimates in the GC positive RA population. Studies on GC use and hip bone strength are limited. In 2007, Burnham and colleagues reported a study on the effects of GC use on bone strength

in a population of children with Crohn's disease and nephrotic syndrome (147). They found that cumulative GC use was inversely associated with outer diameter and section modulus of the femur shaft region (147). Our study did not take into account dosage or cumulative use, which may alter the RA and geometry association, and the truncated sample size hindered statistical power.

As previously stated, the overall goal of hip structure assessment is to provide a more complete picture of bone strength, to aid in the prediction and prevention of fractures. In previous work utilizing HSA, elevations in buckling ratio have been shown in hip fracture cases compared to controls (42, 43), and recently, LaCroix and colleagues found that outer diameter width at the intertrochanteric region was independently associated with a significant increase risk for hip fracture in the entire WHI-BMD cohort (45). Unfortunately, similar analyses could not be performed by RA status, as there were only four hip fractures in the probable RA group at the time of this examination.

Strengths and Limitations

The primary limitations of this study are related to the assessment of RA. The WHI was not designed to be a RA specific study, and RA status is based solely on the respondent. Agreement estimates of self-reported RA to physician diagnoses range from 7-38% (148-152). The method used by Walitt and colleagues in a previous WHI study, showed that coupling medication information with self-report increased the positive predictive value to approximately 60% (100). In the current study, only 14% of the self-reported RA cases indicated one of the medications of interest. The probable RA cases

are probably true RA cases; however, these may represent the more severe cases, which could overestimate the effect of RA on hip strength. Using general RA population prevalence estimates, approximately 1% or 114 women in the WHI-BMD centers should have an RA diagnosis. By using the baseline medication, we potentially captured only 60% of the cases, missing a significant number of likely RA cases. The addition of these unknown cases would provide more unbiased estimates of the associations between RA and hip strength. The WHI also did not collect information on disease duration or severity, which potentially could modify the association between RA and hip strength.

There are also limitations associated with study outcome measurements. Three-dimensional hip structural geometry are being measured from a two-dimensional DXA scan, and several fundamental limitations have been noted (142). For example Khoo and colleagues state that DXA scanners are "optimized to measure mineral mass and not spatial dimensions", hindering the machines ability to precisely measure structural parameters (142). The precision of femur geometry measurements is particularly dependent on subject positioning, much more than conventional BMD (142), making it difficult to reliably detect small changes over time.

Though these limitations have been noted, the WHI ensured the quality of the data with a large number of quality control procedures. As previously stated, the DXA machines used at each of the centers were scanned using calibrated phantoms and any necessary corrections to the machine and clinic procedures were made over the study period. All DXA technicians were trained under manufacturer and WHI protocols, and there is no reason to suggest that the RA patients were positioned differently from the

control group. Dedicated clinic staff also made sure the participants filled out all questionnaires so that complete information on covariates would be available.

The WHI is one of the largest and most diverse cohorts of postmenopausal women in the United States. There is a large ethnic distribution in both the self-reported and probable RA groups compared to the non-arthritic controls, allowing for valuable information on ethnic differences in bone strength and body composition associated with RA to be acquired from this population. There is a wealth of data within the WHI on longitudinal changes in bone strength and as well as information on important RA outcomes such as fractures and cardiovascular outcomes. It provides a good resources to assess the relationship between bone loss and fracture risk in women with RA, as well as the effect the disease has on each of these components over time.

CONCLUSION

Osteoporosis is a significant public health problem for older populations, and highly prevalent in RA populations. Osteoporotic fractures are a result of reduced bone strength, and with the advent of HSA, material and structural properties can be measured, providing a more complete strength estimate. This investigation on RA and its effect on bone strength and changes over time, contributes quality epidemiological findings to the field of rheumatology, which can be used to improve fracture assessment in women with rheumatoid arthritis. Future studies with adequate numbers of confirmed RA cases and fracture outcomes are needed to confirm the additional utility of HSA in the prevention of osteoporotic fractures in these patients.

Table 17: Sample Size and Observation Count by Arthritis Status

Sample Size at Each Study Visit			
	No Arthritis	**Self-Reported RA**	**Probable RA**
Baseline	4,779	453	78
Year 3	3,834	333	49
Year 6	3,447	275	38
Year 9	1,878	132	20
Number of Observations			
	No Arthritis	**Self-Reported RA**	**Probable RA**
1	741	97	25
2	903	109	19
3	2,053	182	22
4	1,308	83	14

Table 18. Baseline Demographics by Rheumatoid Arthritis Status

	No Arthritis (n=4,779)		Self-reported RA (n=453)		Probable RA (n=78)		
	N	%	N	%	N	%	p-value
Baseline Age Group							<0.001
50-59	2,039	42.7	133	29.4	19	24.4	
60-69	1917	40.1	186	41.1	29	27.2	
70-79	823	17.2	134	29.6	30	38.5	
Race/Ethnicity							<0.001
American Indian or Alaskan Native	50	1.1	11	2.4	1	1.3	
Asian or Pacific Islander	20	0.4	2	0.4	0	0.0	
Black or African-American	618	13.0	91	20.1	22	28.6	
Hispanic/Latino	330	7.0	44	9.7	8	10.4	
White (not of Hispanic origin)	3,728	78.6	304	67.3	46	59.7	
Participant of Observational Study							<0.001
No	2,078	43.5	178	39.3	18	23.1	
Yes	2,701	56.5	275	60.7	60	76.9	
Participant of Hormone Trial							0.118
No	3,929	82.2	358	79.0	68	87.2	
Yes	850	17.8	95	20.9	10	12.8	
Participant of CaD Trial							0.003
No	3,676	76.9	365	80.6	71	91.0	
Yes	1,103	23.1	88	19.4	7	9.0	
Participant of Dietary Modification Trial							<0.001
No	3,277	68.6	340	75.1	69	88.5	
Yes	1,502	31.4	113	24.9	9	11.5	
Baseline Hormone Therapy Use							0.214
Never Used	2,370	49.6	225	49.8	33	42.3	
Past User	719	15.1	82	18.1	12	15.4	
Current User	1,688	35.3	145	32.1	33	42.3	

Body Mass Index (BMI) Category							<0.001
Underweight (< 18.5)	43	1.0	2	0.6	1	1.8	
Normal (18.5 - 24.9)	1,420	34.1	96	26.2	15	26.8	
Overweight (25.0 - 29.9)	1,539	367.0	119	32.5	22	39.3	
Obesity i (30.0 - 34.9)	764	18.4	88	24.0	10	17.9	
Obesity ii (35.0 - 39.9)	283	6.8	38	10.4	6	10.7	
Extreme Obesity iii (>= 40)	111	2.7	23	6.3	2	3.6	
Baseline Smoking Status							0.045
Never Smoked	2,608	55.2	246	55.5	34	44.2	
Past Smoker	1,695	35.9	167	37.7	39	50.7	
Current Smoker	420	9.0	30	6.8	4	5.2	

	No RA		**Self-reported RA**		**Probable RA**		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-value**
Age (years)	61.69	7.36	64.61	7.73	65.36	7.50	<0.001
Height (cm)	161.90	6.41	160.70	6.16	161.30	5.71	0.001
Weight (kg)	72.16	15.5	77.00	18.66	74.65	15.80	<0.001
BMI (kg/m2)	27.44	5.50	29.50	6.24	28.65	5.54	<0.001
Total Energy Expended per Week (METs)	12.32	14.59	11.04	14.77	11.66	16.45	0.203
Physical Function	85.92	16.39	69.60	23.08	53.77	25.03	<0.001
Dietary Energy (kcal)	1,644.05	836.28	1,699.00	1096.00	1540.00	717.20	0.234
Total Calcium (mg)	1,087.68	707.57	1,163.00	804.9	1198.00	915.60	0.048
Total Vitamin D (IU)	7.89	6.66	8.59	7.28	8.53	7.28	0.081

Table 19: Cross-sectional Examination of BMD and Hip Structural Geometry by Arthritis Status at the Narrow Neck Region

	No RA (n=4,779)		Self-reported RA (n=453)		Probable RA (n=78)		
	Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**	**p-value**
BMD (g/cm^2)							
Baseline	0.715	0.002	0.747	0.006	0.705	0.014	A, C
Year 3	0.725	0.002	0.751	0.007	0.695	0.018	A, C
Year 6	0.715	0.002	0.744	0.008	0.701	0.021	A
Year 9	0.701	0.003	0.726	0.010	0.666	0.026	A, C
OD (cm)							
Baseline	2.999	0.003	3.013	0.010	3.044	0.024	
Year 3	3.015	0.004	3.040	0.012	3.033	0.032	
Year 6	3.027	0.004	3.053	0.014	3.010	0.037	
Year 9	3.068	0.005	3.062	0.020	3.002	0.050	
CSA (cm^2)							
Baseline	2.037	0.005	2.137	0.016	2.041	0.039	A, C
Year 3	2.075	0.006	2.170	0.020	2.006	0.053	A, C
Year 6	2.055	0.006	2.154	0.023	2.005	0.061	A, C
Year 9	2.042	0.008	2.110	0.030	1.904	0.078	A, C
SM (cm^3)							
Baseline	0.905	0.003	0.956	0.009	0.922	0.021	A
Year 3	0.934	0.003	0.991	0.011	0.904	0.030	A, C
Year 6	0.931	0.004	0.987	0.013	0.920	0.034	A
Year 9	0.933	0.005	0.966	0.017	0.870	0.043	C
BR							
Baseline	12.398	0.038	11.900	0.125	12.807	0.299	A, C
Year 3	12.346	0.044	11.972	0.148	12.981	0.386	A, C
Year 6	12.603	0.048	12.135	0.170	12.978	0.455	A
Year 9	13.056	0.065	12.580	0.242	13.580	0.621	

A: $p<0.05$ between No Arthritis and Self-Reported RA
B: $p<0.05$ between No Arthritis and Probable RA
C: $p<0.05$ between Self-reported RA and Probable RA
BMD=Bone Mineral Density; OD=Outer Diameter; CSA=Cross-Sectional Area; SM=Section Modulus; BR=Buckling Ratio

Table 20: The Association between Arthritis and BMD and Hip Structural Geometry based on Random Coefficient Model by Region

	Narrow Neck		Intertrochanteric		Shaft	
	coef.	**(95% CI)**	**coef.**	**(95% CI)**	**coef.**	**(95% CI)**
BMD						
No Arthritis	Ref.		Ref.		Ref.	
Self-Reported RA	-0.003	(-0.008, 0.003)	0.002	(-0.003, 0.007)	0.001	(-0.007, 0.009)
Probable RA	**-0.016**	**(-0.030, -0.002*)**	-0.006	(-0.019, 0.008)	-0.005	(-0.025, 0.015)
OD						
No Arthritis	Ref.		Ref.		Ref.	
Self-Reported RA	0.000	(-0.011, 0.011)	0.008	(-0.009, 0.026)	0.002	(-0.006, 0.011)
Probable RA	**-0.034**	**(-0.063, -0.006*)**	0.003	(-0.040, 0.046)	-0.006	(-0.027, 0.015)
CSA						
No Arthritis	Ref.		Ref.		Ref.	
Self-Reported RA	-0.008	(-0.025, 0.009)	0.014	(-0.011, 0.040)	0.007	(-0.014, 0.028)
Probable RA	**-0.069**	**(-0.111, -0.028**)**	-0.024	(-0.087, 0.038)	-0.019	(-0.071, 0.033)
SM						
No Arthritis	Ref.		Ref.		Ref.	
Self-Reported RA	-0.002	(-0.012, 0.008)	0.015	(-0.013, 0.043)	0.008	(-0.006, 0.021)
Probable RA	**-0.029**	**(-0.054, -0.003*)**	-0.039	(-0.106, 0.028)	-0.020	(-0.054, 0.015)
BR						
No Arthritis	Ref.		Ref.		Ref.	
Self-Reported RA	0.048	(-0.085, 0.180)	-0.054	(-0.158, 0.051)	-0.012	(-0.052, 0.028)
Probable RA	0.227	(-0.104, 0.558)	0.157	(-0.098, 0.412)	0.038	(-0.062, 0.139)

All models adjusted for visit, baseline hip strength parameter, age, ethnicity, center, height, weight, total body % lean mass, CaD Trial arm, HT trial arm, hormone use, anticonvulsant medication usage, and osteoporosis medication usage

* $p<0.05$

**$p<0.01$

BMD=Bone Mineral Density; OD=Outer Diameter; CSA=Cross-Sectional Area; SM=Section Modulus; BR=Buckling Ratio

Table 21: Mean (SD) Narrow Neck BMD and Hip Geometry Measures by RA and Glucocorticoid Use Status at Baseline

	$RA^{--}GC^{--}$ (n=4,755)	$RA^{--}GC^{++}$ (n=24)	$RA^{++}GC^{--}$ (n=42)	$RA^{++}GC^{++}$ (n=36)	p-value[a]
BMD (g/cm2)	0.717 (0.128)	0.686 (0.106)	0.685 (0.130)	0.681 (0.130)	0.076
CSA (cm2)	2.042 (0.363)	2.014 (0.505)	2.008 (0.388)	1.961 (0.381)	0.514
OD (cm)	2.998 (0.212)	3.063 (0.344)	3.082 (0.196)	3.026 (0.188)	0.027[b]
SM (cm3)	0.907 (0.190)	0.945 (0.454)	0.920 (0.195)	0.879 (0.204)	0.596
BR	12.351 (2.853)	13.111 (2.324)	13.345 (3.181)	13.262 (3.010)	0.017 [b]

[a] p-values based on ANOVA F-test

[b] overall F-test significant, but no significant associations in Bonferroni post-hoc analyses

RA: rheumatoid arthritis; CG: glucocorticoid; BMD: bone mineral density; CSA: cross-sectional area; OD: outer diameter; SM: section modulus; BR: buckling ratio

Table 22: Longitudinal Association of Narrow Neck BMD and Hip Geometry by RA and Glucocorticoid Use using the Random Coefficient Model

	coef.	95% CI
BMD		
RA^{--} GC^{--}	Ref.	
RA^{--} GC^{++}	-0.003	(-0.026, 0.020)
RA^{++} GC^{--}	-0.015	(-0.031, 0.001)
RA^{++} GC^{++}	-0.018	(-0.040, 0.003)
CSA		
RA^{--} GC^{--}	Ref.	
RA^{--} GC^{++}	0.003	(-0.065, 0.070)
RA^{++} GC^{--}	**-0.072**	**(-0.118, -0.025)***
RA^{++} GC^{++}	**-0.065**	**(-0.126, -0.004)***
OD		
RA^{--} GC^{--}	Ref.	
RA^{--} GC^{++}	0.011	(-0.039, 0.062)
RA^{++} GC^{--}	**-0.041**	**(-0.073, -0.009)***
RA^{++} GC^{++}	-0.017	(-0.063, 0.029)
SM		
RA^{--} GC^{--}	Ref.	
RA^{--} GC^{++}	0.001	(-0.041, 0.044)
RA^{++} GC^{--}	**-0.033**	**(-0.061, -0.005)***
RA^{++} GC^{++}	-0.020	(-0.059, 0.018)
BR		
RA^{--} GC^{--}	Ref.	
RA^{--} GC^{++}	0.200	(-0.354, 0.753)
RA^{++} GC^{--}	0.215	(-0.163, 0.593)
RA^{++} GC^{++}	0.264	(-0.239, 0.766)

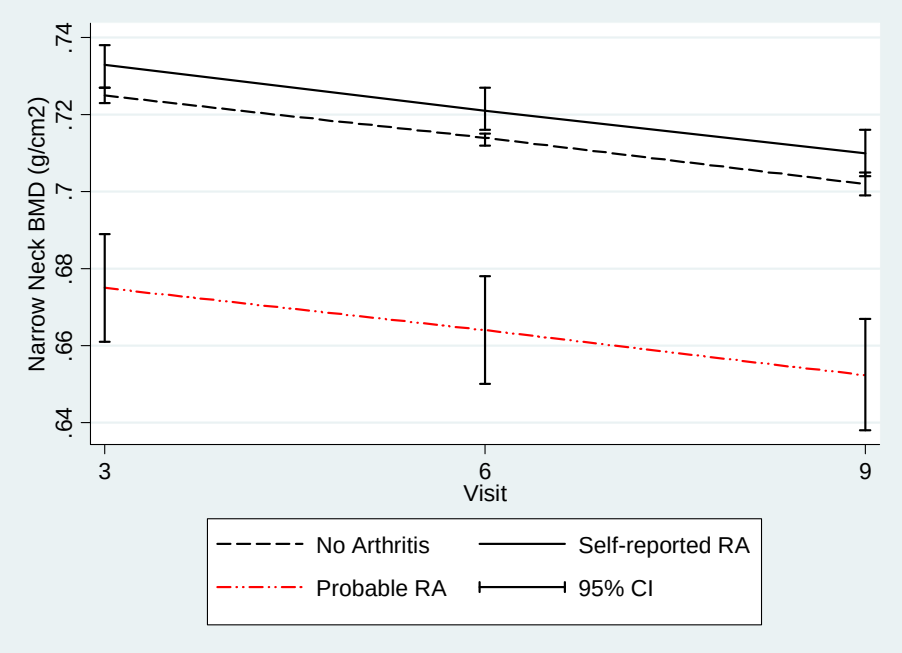
* $p<0.05$

All models adjusted for visit, baseline hip strength parameter, age, ethnicity, center, height, weight, total body % lean mass, CaD Trial arm, HT trial arm, hormone use, anticonvulsant medication usage, and osteoporosis medication usage

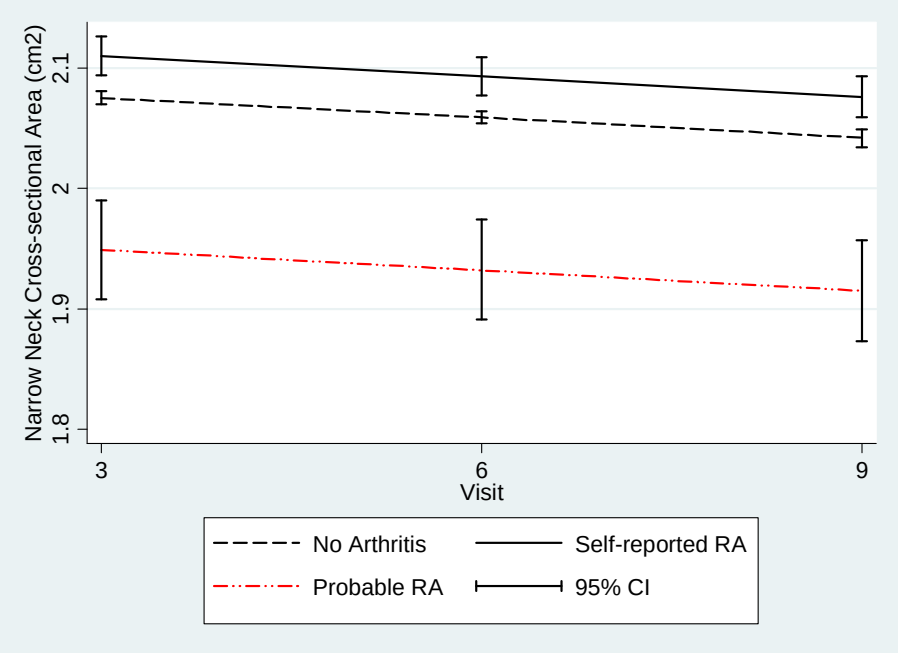
RA: rheumatoid arthritis; CG: glucocorticoid; BMD: bone mineral density; CSA: cross-sectional area; OD: outer diameter; SM: section modulus; BR: buckling ratio

Figure 4: Longitudinal Changes in BMD and Hip Structural Geometry by Arthritis Status

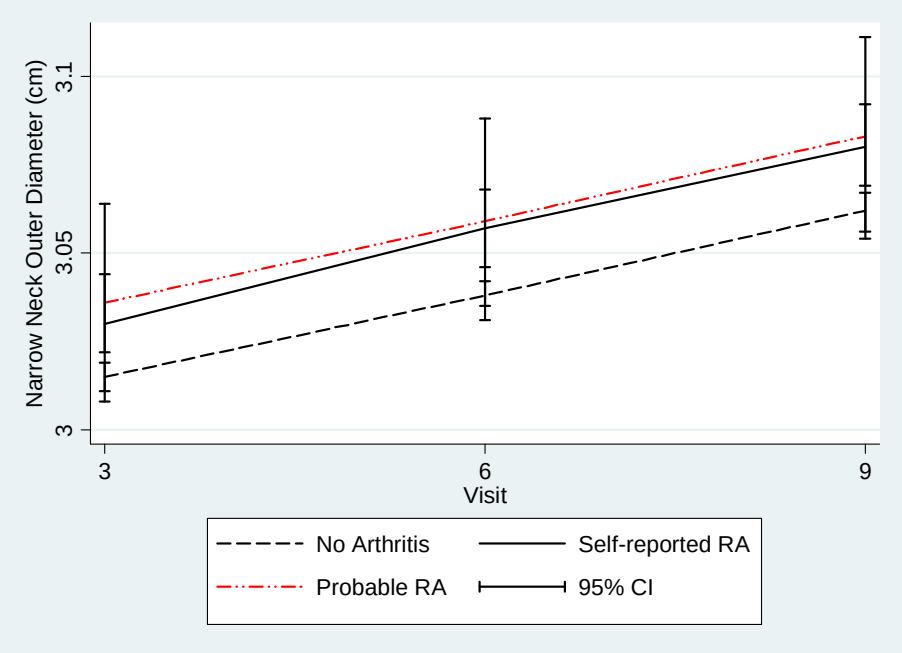
A: Bone Mineral Density



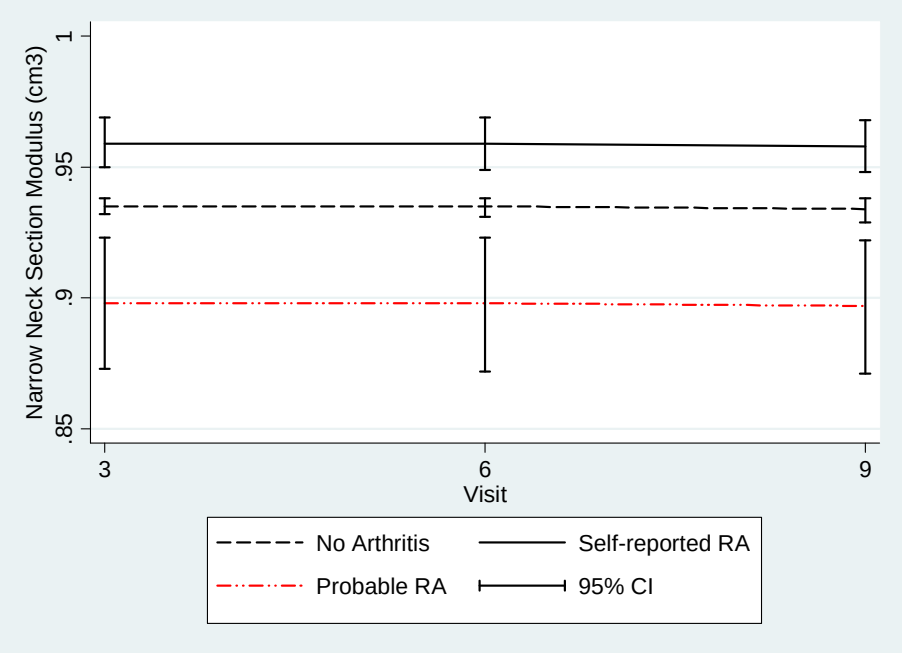
B: Cross-Sectional Area



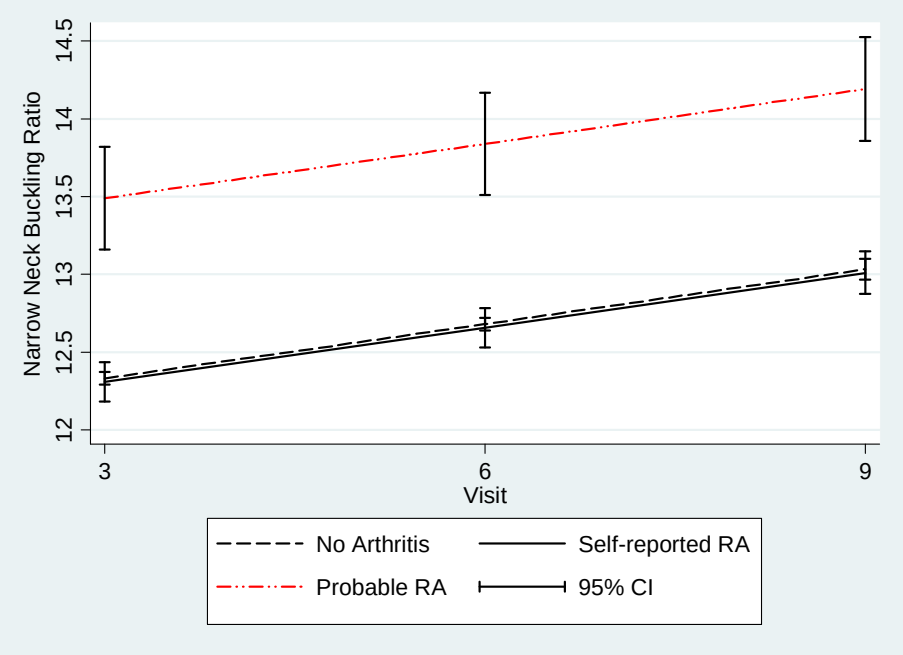
C: Outer Diameter



D: Section Modulus



E: Buckling Ratio



*Mean values predicted after adjustment for individual baseline strength value, population mean for the continuous variables (age, height, weight, and percent lean) and mean proportion of the continuous variables (ethnicity, center, participation in CaD and HT, hormone therapy use, anticonvulsant use, and osteoporisis medication use.

CHAPTER 9: THE ASSOCIATION BETWEEN RHEUMATOID ARTHRITIS AND BODY COMPOSITION

INTRODUCTION

Skeletal muscle mass and its maintenance are both extremely important for a variety of health outcomes, including bone health. Significant reductions in skeletal muscle are associated with functional deterioration, changes in metabolism, and an increased fracture risk among aging populations (62, 153-156). Cachexia, a common condition in rheumatoid arthritis (RA), is characterized by loss of fat-free mass and an increase of fat mass in the presence of a stable body weight (5, 18). Rheumatoid cachexia compromises muscle strength and functional capacity, and is a significant contributor to reduced life expectancy in RA patients (5, 18).

Rheumatoid cachexia has been studied using a variety of body composition assessment methods. Studies have shown that RA patients have between 0-12% lower estimates of dual energy X-ray absorptiometry (DXA)-derived estimates of lean mass compared to controls (87-89). The opposite is true in regards to fat mass, with studies showing female RA patients had a higher DXA-derived mean total fat, percent fat, and fat mass index than controls (95). Similar results have been found using other body composition assessment methods, for example, Stavropoulos-Kalinoglou found that for a given BMI, RA patients had 4.3% more BIA-estimated fat mass than controls (91).

Osteoporosis, a common co-morbidity in RA, has strong associations with body composition. The decrease in lean mass and increase in fat mass experienced by RA patients can negatively affect bone health, further increasing the risk for disability and/or

fractures in this already high-risk population. To date, most of the body composition studies in RA are cross-sectional in nature, and there are very few studies on the longitudinal changes in body composition in a racially diverse group of RA patients. The main goal of this analysis is to longitudinally assess body composition in postmenopausal women reporting RA compared to postmenopausal women not reporting any arthritis condition in the participants of the nationwide Women's Health Initiative.

METHODS

The participants of the WHI-BMD centers were also used for this study. As previously stated, the women enrolled in the BMD centers (n=11,020) received DXA scans on a Hologic QDR 2000 or 4500W machine (Hologic; Waltham MA) to measure bone density at the spine, areal hip, and total body; in addition to whole body and regional body composition. The scans were completed at baseline, years 3, 6, and 9 for participants of the OS; and baseline, years 1, 3, 6, 9, and closeout of the study for CT participants.

For these analyses, only two arthritis groups were used: the non-arthritis control group and the probable RA group. The women not reporting arthritis on the baseline health questionnaire were used as the non-arthritic control reference group, and the probable RA group consisted of the women who self-reported RA and at least one commonly used disease therapeutic agent. Those who did not respond to the baseline arthritis question, reported other arthritic conditions, or self-reported RA without at least one DMARD were excluded.

Body Composition Assessment

Trained DXA technicians performed the DXA scans at each center, paying special attention to placement of the participants to have adequate longitudinal assessments. DXA quality control, including monitoring DXA operator performance, DXA machine performance, and managing DXA databases, of the three WHI-BMD centers was monitored by the WHI center at the University of California, San Francisco (UCSF Prevention Sciences, San Francisco, CA). Three Hologic spine, hip, and linearity phantoms were exchanged among the centers to assess quality control and cross-calibration.

Whole body and regional lean soft tissue mass (LSTM) and fat mass (FM) were estimated by DXA using Hologic software (version 7.2-8 for QDR 2000 machines and version 9.02 & 9.8 for QDR 4500 machines). Regional measures included arm, trunk (mid-section), and legs. Body composition estimates from arms and legs were combined to create appendicular body composition variables. Absolute (kg) body composition measures (LSTM and FM) in addition to relative (%LSTM and %FM) were reported by DXA. Relative body composition measures were created by dividing the absolute value by total body mass (TBM) and expressing as a percent (ie. [FM(kg)/TBM(kg)]*100). The following variables were used in this analysis: TBM; total body absolute LSTM and FM; total body %LSTM and %FM; and appendicular absolute LSTM and FM.

Covariates

The following baseline variables were tested as covariates in the association between RA and body composition: age, height, weight, race/ethnicity, hormone use, smoking status, alcohol use, physical activity, dietary energy, hospitalizations, the presence of selected co-morbidities, and randomization status in the WHI clinical trial arms. Age in years was reported at screening. Height (cm) and weight (kg) were measured at screening clinic visits by WHI clinical staff using standardized procedures. Race and ethnicity was classified into 6 categories: American Indian or Alaskan native, Asian or Pacific Islander, African American, Hispanic or Latino, White (not of Hispanic origin), or other. Summary variables for hormone use (never, past, or current user), smoking (never, past, or current smoker), alcohol use (never, past, and number of drinks per week/month), and the number of times hospitalized in the last two years were created using questionnaire responses. Metabolic equivalent units (METs) were assigned to the reported physical and leisure activities, and a total energy expenditure per week variable was created. Total energy intake was based on responses to the WHI Food Frequency Questionnaire. Co-morbidities of interest included history of hypertension, cancer (any cancer type), thyroid gland problems (over or under active), and cardiovascular diseases (including coronary heart failure, cardiac catherization, coronary bypass surgery, angioplasty of coronary arteries, atrial fibrillation, angina, and peripheral arterial disease).

Statistical Analysis

Baseline characteristics were compared between the no arthritis and probable RA group using t-tests for continuous variables and X^2 test for categorical variables. Age-adjusted body composition by visit was estimated and compared between the two groups using linear regression for a preliminary cross-sectional analysis. The longitudinal association between RA and body composition was assessed using two methods: 1) percent change in body composition from baseline to year 6, and 2) random coefficient model (RCM). The percent change between baseline and year 6 body composition was calculated ([(baseline body composition-year 6 body composition)/baseline body composition]*100) and used as the dependent variable in the linear regression models. The RCM, a type of linear mixed effects models that allows for the incorporation of all time points (for example baseline, year 3, and year 6 in this study) in one model, was used to control for serial correlation in the data by fitting a slope and intercept within each subject. The slope and intercepts terms fitted within subjects were included as random effects in the mixed effects models.

The independent effect of each covariate and age was examined in the association between RA and body composition for each longitudinal method (% change and RCM). Interactions between visit, age, and race/ethnicity were tested. Variables with a p-value <0.2 in the marginal analyses were included as variables to build the final models. Confounding was assessed by examining the change in magnitude of the RA coefficient with the inclusion and exclusion of the specific covariate being tested. Variables that were statistically significant and resulted in a $\geq 10\%$ change in the RA coefficient when

removed from the model, were included as confounders. Variables that were statistically significant and did not confound (ie change the RA coefficient <10%) were removed from the model. The final model included variables that were related to WHI design, biologically meaningful, or confounded the RA and body composition association. All analyses were performed using STATA v.10 (College Station, TX).

RESULTS

Of the 11,020 women enrolled in the WHI-BMD, body composition was available on 5074 women who did not report arthritis and 82 of the women in the probable RA group. The probable RA group was significantly older (3.8 years on average) than the non-arthritic control group, and the racial and ethnic distribution was significantly different between the two groups, with the proportion of African Americans in the probable RA group being 25% compared to only 13% in the non-arthritic control group (Table 23). The probable RA group was heavier than the non-arthritic control group (2 kg on average), however this difference was not statistically significant. More of the non-arthritic control group participated in the CT, however, there were statistically more participation in the women without arthritis in the DM and CaD trials.

Several lifestyle factors were statistically different between the two groups. The probable RA group had a higher percentage of past smokers (49.4% vs 36.2%), whereas the non-arthritic control group had a higher percentage of current smokers (9.0% vs 4.9%). Statistically more women in the probable RA group had hypertension, cardiovascular diseases, and hospitalization than the non-arthritic control group. There

were no statistically significant differences in hormone therapy use, energy intake or energy expenditure (Table 23).

Cross-sectional Examination of Body Composition

The age-adjusted cross-sectional analysis revealed several differences in body composition at baseline. Total body mass measured by DXA was higher (3.5 kg on average) in the probable RA group compared to the non-arthritis group. The probable RA group had statistical higher absolute and relative measures of FM than the non-arthritic control group. Total body FM was on average 3.4 kg higher (p=0.004); appendicular fat mass was 1.6 kg higher (p=0.007), and the probable RA group had on average 2.47% (p=0.002) more FM than the non-arthritic control group (Table 24).

Neither absolute total body nor appendicular LSTM were statistically different between the two groups at baseline; however, the probable RA group had 2.43 lower %LSTM (LSTM relative to mass) than the non-arthritic group (p=0.002). There were also no statistically significant differences in absolute LSTM or total body mass at years 3 and 6. Significant differences between the two groups at years 3 and 6 in the age-adjusted body composition values were only observed in the relative measures, with the probable RA group having on average a 2.3% decrease in %LSTM and 2.3% increase in %FM at each time point compared to the non-arthritic control group (Table 24).

Longitudinal Examination of Body Composition

The marginal analysis revealed several of the covariates were significantly associated with body composition, however the final longitudinal models were adjusted for the following baseline covariates: age, height, ethnicity, participation in the HT or DM (not randomized, placebo, or intervention), smoking, hormone use, alcohol use, total energy expenditure per week, and hypertension. In addition, weight was adjusted for in models with absolute LSTM and FM as outcomes. There were no significant interactions between RA and age or ethnicity on body composition in either the percent change or RCM models; and no differential effect in the association between RA and body composition was seen by time.

The percent change analysis revealed no statistically significant difference between RA and six-year change in body composition; including TBM, total body and regional absolute LSTM and FM, in the crude or adjusted analyses. Using all observations (baseline, year 3 and year 6), the RCM revealed no statistically significant differences in total mass between the two groups, but did reveal several differences in body composition between the probable RA and non-arthritic control group. After adjusting for the covariates and weight, on average the probable RA group had significantly less total body [coef (95% CI)] [-0.88 (-1.54, -0.21)] and appendicular LSTM [-0.72 (-1.07, -0.36)] and significantly more total body FM [1.41 (0.57, 2.25)] over the study period when compared to the non-arthritis control group (Table 25). Similarly, the probable RA group had significantly lower %LSTM [-2.31 (-3.75, -0.87)] and higher %FM [2.37 (0.87, 3.87)] than the non-arthritic control group after adjusting

for the covariates (Table 25). Using the results from the RCM, mean body composition values were plotted at each time point based on adjustment for the population mean for continuous variables (age, height, weight (if used), and total energy expended from physical activity) and mean proportions of the categorical variables (ethnicity, CT participation, smoking, hormone therapy use, alcohol category, and hypertension) (Figure 5).

DISCUSSION

In this study of body composition in postmenopausal women with and without reports of RA, it was found that after adjusting for age, weight, and several other demographic and lifestyle variables, the probable RA group has less LSTM and more FM compared to the women without reports of arthritis. Similarly, women with probable RA have less LSTM and more FM relative to weight (%LSTM & % FM) than women without arthritis. The findings were irrespective of baseline age and time, and though there were significant racial distribution differences between the two groups, there were no statistically significant different effects of RA on body composition by ethnicity.

This study agrees with the rheumatoid cachexia definition proposed by Rubenoff with the probable RA group on average having less %LSTM and more %FM than controls. Lower estimates of lean mass (85, 87-89, 157), and higher estimates of fat mass (85, 90, 91, 95) in RA compared to controls have been reported by several groups, and the findings of this study are comparable to the previous reports. of both lean and fat

mass in RA.. Though Giles and colleagues found higher estimates of fat mass in female RA patients, they did not find reductions in lean mass in their population (95).

Disuse of muscles, as a result of joint pain and damage, may contribute to loss of skeletal muscle; however, the primary mechanism behind cachexia in RA is inflammation, and similar to their degrading role in bones, several inflammatory cytokines play a negative role in skeletal muscle (5). Inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and IL-1β, are believed to be the mediators in muscle loss. These cytokines have been shown to shift protein metabolism toward net catabolism, altering the balance between protein degradation and synthesis (5). As an inflammatory condition, RA patients have higher levels of the pro-inflammatory cytokines than various control populations (158), and the relationship between inflammation and lean mass has been assessed in RA patients. For example, in a small Swedish study, Engvall and colleagues found that IL-6 was negatively correlated with lean body mass in RA patients (159).

In non-RA cohorts, several studies have shown that increases in the pro-inflammatory cytokines are associated with decreases in muscle mass and strength. For example in the women of Health ABC, lower grip strength and lower knee extensor strength was observed in those with elevated levels of IL-6 and TNF-α compared to women with normal cytokine levels (160). Similarly, Barbieri and colleagues found that higher levels of IL-6 was significantly associated with lower muscle strength and power (161). Increases in IL-6 lead to increased production of C-reactive protein (CRP) in the liver. These authors hypothesized that inflammation inhibits the synthesis of important

growth factors, such as insulin-like growth factor-1 (IGF-1) (161), which is needed to maintain skeletal muscle. This hypothesis was also suggested in the Engvall study as they found inflammation was negatively correlated with bioavailable IGF-1 as measured by the ratio of IGF-1 to IGF binding protein-1 (IGFBP-1) (159).

Inflammation and adipose tissue also have an interesting relationship. Not only does adipose tissue promotes low-grade systemic inflammation by producing pro-inflammatory molecules (i.e IL-6, TNF-α, IL-1β, etc.), but inflammation may also promote dysfunction or over production of inflammatory cytokines in adipose tissue (162-164). Correlations between inflammatory markers and fat mass have been shown in healthy controls and a variety of disease states. Using the NHANES-III data, Visser and colleagues found (in women more than men) higher levels of circulating CRP in those with a BMI ≥30 than in those with a BMI <25 (165). Higher levels of CRP and soluble TNF receptor-1 (sTNFR-1) were associated with a higher mean fat mass index in COPD patients (162), and Faber and colleagues recently reported that intra-abdominal fat is associated with higher levels of CRP in patients with atherosclerotic disease (163).

In RA populations, associations between inflammation and fat mass have also been studied. Giles et al (2008) found a positive association between trunk fat and CRP, specifically in RA patients with higher estimates of trunk fat had higher circulating levels of CRP (166). Similarly, Stavropoulous-Kalinoglou et al found after adjusting for several variables that body fat, measured by BIA, was significantly associated with CRP and erythrocyte sedimentation rate (ESR), a marker of inflammation, in RA patients (167).

Rheumatoid cachexia and other muscle wasting conditions are associated with poor disease outcomes. Giles followed up their initial evaluation on body composition in RA to see how it influences disability. Using the Health Assessment Questionnaire (HAQ), they found that higher appendicular fat mass was associated with a higher HAQ score (indicating more disability), and inversely, higher appendicular lean mass was associated with lower HAQ scores (indicating less disability) (96). This effect was more prominent in women, but men followed a similar trend. Stavropoulos-Kalinoglou and colleagues also found that body fat was associated with a higher HAQ score in their study of British RA patients (167), further suggesting that inflammation-associated changes in body composition are associated with poor disease outcomes.

Strengths and Limitations

Unlike many of the other body composition studies within RA, this study was able to longitudinally assess the association in a multi-ethnic cohort of women, providing more evidence that RA is causally associated with changes in body composition than the findings of cross-sectional studies. Potentially due to the small sample size, no statistically significant modification in the association between RA and body composition by ethnicity was found; however, when stratified by ethnicity the magnitude of the decrease in LSTM and increase in FM at baseline was higher in African American women with RA compared to the non-Hispanic white women.

The use of DXA-derived body composition is another strength of this study. Though not the gold standard, DXA can accurately measure body composition and

changes in body composition. A comparative study was performed in a sub-sample of the WHI and found that DXA-derived LSTM has excellent correlation with MRI derived estimates of skeletal muscle mass (168), and previous longitudinal body composition studies have found that though there are discrepancies, DXA can adequately assess change in body composition over time (169). With the use of a large cohort like the WHI, this study was able to adjust for several factors that are related to body composition that other studies are not able to, again adding to its strengths.

However, this study is not without limitations. Like in the previous chapters (7-8), the primary limitation of this study is related to the RA exposure classification. Validity estimates of self-reported RA range from 7-38% (148-152). The method used to define the probable RA category by Walitt and colleagues in a previous WHI study, showed that coupling medication information with self-report increased the positive predictive value from 14 to 62% (100). Though small in number, the probable RA cases within the WHI-BMD are probably true RA cases; however, these may represent the more severe cases, which could overestimate the effect of RA on body composition. Inflammation is a primary driver of the association between RA and body composition, and without information on disease duration or severity, factors highly related to inflammation exposure, the potential modification of disease duration or severity was not examined, potentially biasing the results of this study.

Conclusions

Though limited, this is one of the first studies examining the association between body composition longitudinally, and confirms that RA is associated with decreases in lean mass and increases in fat mass. This information can assist clinicians in suggesting appropriate diet and physical activity measures to minimize or prevent the disability, osteoporotic fractures, and other adverse consequences from poor body composition in older postmenopausal RA patients.

Table 23. Baseline Characteristics by Arthritis Status

	No Arthritis (n=5,074)		Probable RA (n=82)		
	N	**%**	**N**	**%**	**p-value**
Baseline Age Group					<0.001
50-59	2,184	43.0	20	24.4	
60-69	2,033	40.1	28	34.2	
70-79	857	16.9	34	41.5	
Ethnicity					0.013
White	3,955	78.1	51	62.2	
Black	665	13.1	21	25.6	
Hispanic	343	6.8	8	9.8	
American Indian/Alaskan Native	55	1.1	1	1.2	
Asian/Pacific Islander	23	0.5	0	0.0	
Other	24	0.5	1	1.2	
Hormone Trial					0.200
Not randomized	4,165	82.1	72	87.8	
Intervention	480	9.5	3	3.7	
Placebo	429	8.5	7	8.5	
Calcium and Vitamin Trial					0.006
Not randomized	3,892	76.7	75	91.5	
Intervention	591	11.6	2	2.4	
Control	591	11.6	5	6.1	
Dietary Modification Trial					<0.001
Not randomized	3,467	68.3	73	89.0	
Intervention	625	12.3	4	4.9	
Control	982	19.4	5	6.1	
Smoking Status					0.038
Never smoked	2,751	54.8	37	45.7	
Past smoker	1,814	36.2	40	49.4	
Current smoker	451	9.0	4	4.9	
Hormone Therapy Use					0.443

Never used	2,509	49.5	35	42.7	
Past user	770	15.2	13	15.9	
Current user	1,793	35.4	34	41.5	
Alcohol Use					0.017
Non drinker	799	15.9	17	21.0	
Past drinker	968	19.2	25	30.9	
1-4 drinks/month	1,710	33.9	25	30.9	
1-7 drinks/week	1,133	22.5	10	12.3	
7+ drinks/week	429	8.5	4	4.9	
Hypertension Ever					<0.001
No	3,582	71.0	40	51.3	
Yes	1,460	29.0	38	48.7	
Hospitalized Overnight During Last 2 Years					0.001
No	3,837	87.6	59	74.7	
Yes	544	12.4	20	25.3	
Thyroid Gland Problem Ever					0.208
No	4,018	79.8	60	74.1	
Yes	1,020	20.2	21	25.9	
Cancer Ever					0.067
No	4,715	93.8	71	88.8	
Yes	313	6.2	9	11.3	
Cardiovascular Disease Ever					<0.001
No	3,681	82.6	52	65.0	
Yes	775	17.4	28	35.0	

	Mean	**SD**	**Mean**	**SD**	**p-value**
Age at Screening (years)	61.6	7.3	65.5	7.6	<0.001
Height (cm)	161.9	6.4	161.4	5.9	0.433
Weight (kg)	72.2	15.5	74.1	16.0	0.255
Total Energy Expended per week (METs)	12.4	14.7	11.5	16.1	0.609
Dietary Energy Intake (kcals)	1,645.0	832.5	1,539.0	709.1	0.252

Table 24: Age-Adjusted Body Composition by RA Status Over the Study Period

	No RA (n=5,074)		Probable RA (n=82)		
	Mean	**SE**	**Mean**	**SE**	**p-value**
Total Body Mass (kg)					
Baseline	70.55	0.20	74.05	1.59	0.029
Year 3	70.62	0.22	73.71	1.94	0.113
Year 6	70.80	0.23	71.94	2.25	0.616
Total Body LSTM (kg)					
Baseline	37.48	0.07	37.50	0.56	0.975
Year 3	37.18	0.08	37.04	0.67	0.831
Year 6	37.16	0.08	35.97	0.76	0.124
Total FM (kg)					
Baseline	31.04	0.15	34.45	1.19	0.004
Year 3	31.40	0.17	34.58	1.46	0.031
Year 6	31.63	0.17	33.93	1.69	0.177
Appendicular LSTM (kg)					
Baseline	14.92	0.04	14.77	0.30	0.629
Year 3	14.72	0.04	14.46	0.36	0.465
Year 6	14.48	0.04	13.76	0.40	0.073
Appendicular FM (kg)					
Baseline	15.90	0.08	17.51	0.59	0.007
Year 3	16.09	0.08	17.69	0.74	0.032
Year 6	16.40	0.09	17.26	0.86	0.320
Total Body %LSTM					
Baseline	54.16	0.10	51.73	0.77	0.002
Year 3	53.72	0.11	51.18	0.94	0.008
Year 6	53.57	0.11	51.35	1.08	0.041
Total Body %FM					
Baseline	42.91	0.10	45.38	0.80	0.002
Year 3	43.35	0.11	45.90	0.98	0.010
Year 6	43.52	0.12	45.75	1.13	0.049

LSTM= lean soft tissue mass; FM = fat mass

Table 25: Longitudinal Association between RA and Body Composition using the Random Coefficient Model

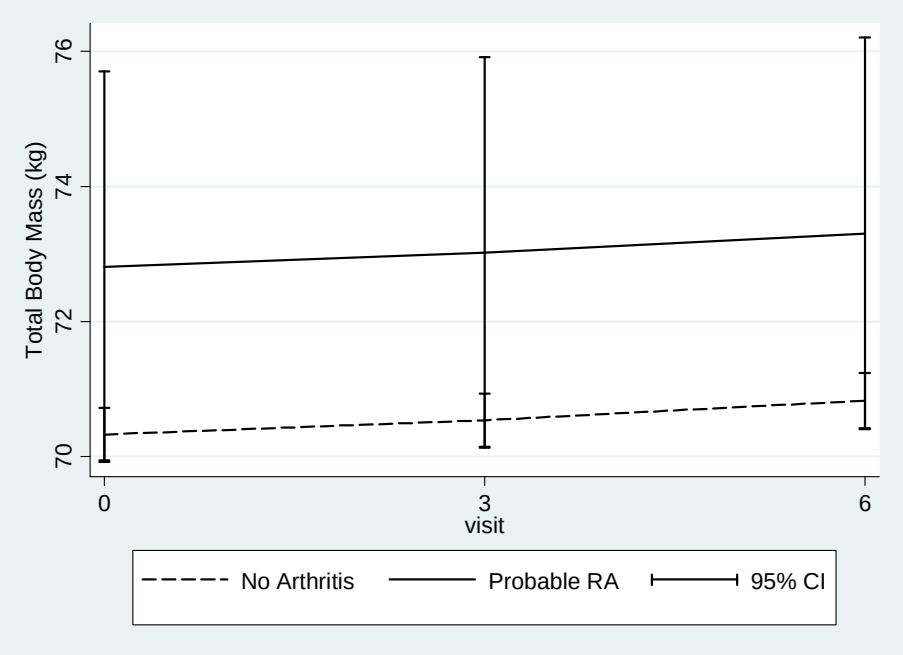
	Coef.	SE	p-value	95% CI
Total Body Mass (kg)				
No Arthritis (n=5,074)	Ref.			
RA (n=82)	2.48	1.49	0.095	(-0.43, 5.39)
Total Body LSTM (kg)				
No Arthritis	Ref.			
RA	-0.88	0.34	0.010	(-1.54, -0.21)
Total Body FM (kg)				
No Arthritis	Ref.			
RA	1.41	.43	0.001	(0.57, 2.25)
Appendicular LSTM (kg)				
No Arthritis	Ref.			
RA	-0.72	0.18	<0.001	(-1.07, -0.36)
Appendicular FM (kg)				
No Arthritis	Ref.			
RA	0.55	0.31	0.076	(-0.06, 1.15)
Total Body %LSTM				
No Arthritis	Ref.			
RA	-2.31	0.73	0.002	(-3.75, -0.87)
Total Body %FM				
No Arthritis	Ref.			
RA	2.37	0.76	0.002	(0.87, 3.87)

***** Adjusted for visit, age, height, weight (absolute body composition models only), ethnicity, participation in CT (not randomized, placebo, intervention), smoking, hormone use, alcohol use, total energy expenditure per week, and hypertension

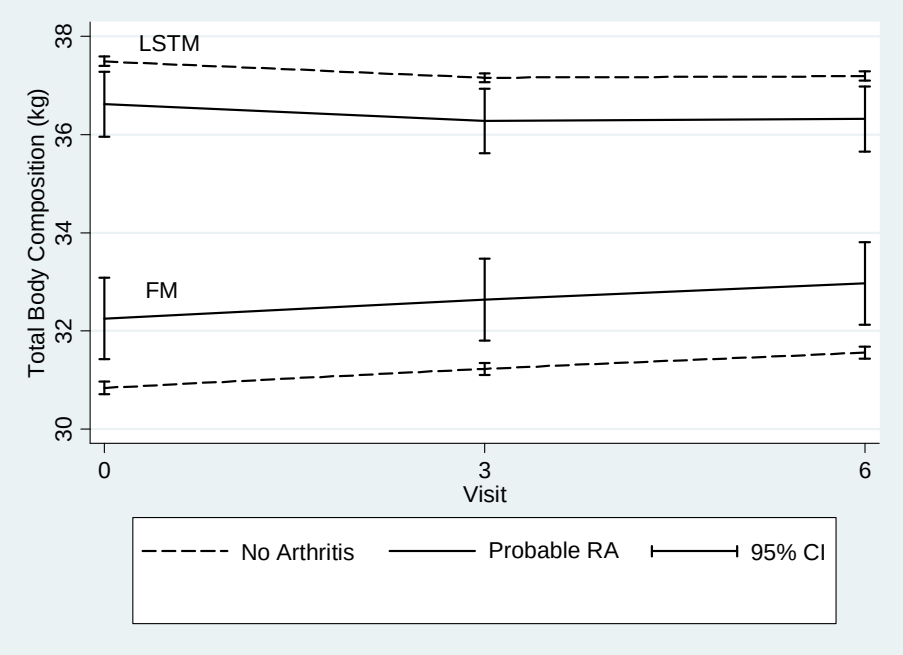
LSTM = lean soft tissue mass; FM = Fat Mass

Figure 5: Predicted Longitudinal Body Composition by RA status

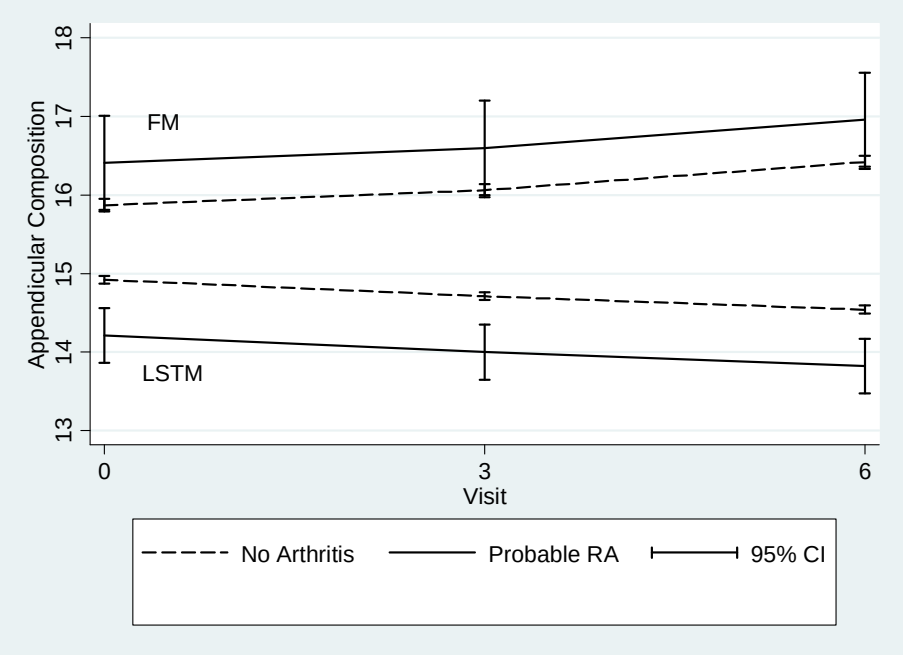
A: Total Body Mass (kg)



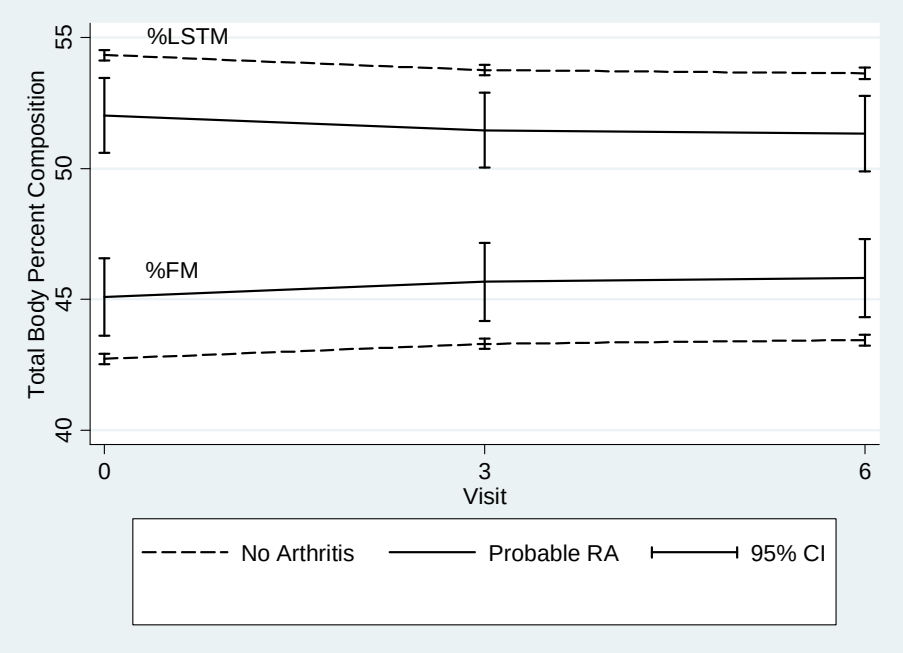
B: Total Body Lean and Fat Mass (kg)



C: Appendicular Lean & Fat Mass (kg)



D: Total Body % Lean & Fat Mass



* Mean body composition values were predicted from the RCM models using the population mean for continuous variables (age, height, weight (if used), and total energy expended from physical activity) and mean proportions of the categorical variables (ethnicity, CT participation, smoking, hormone therapy use, alcohol category, and hypertension)

LSTM- lean soft tissue Mass; FM- fat mass; RA- rheumatoid arthritis; 95% CI- 95% confidence interval

CHAPTER 10: OVERALL CONCLUSIONS

The findings from the studies on the participants of the WHI show that, RA, as defined by the self-report of RA plus report of a DMARD or glucocorticoid, is associated with an increase in fracture risk, a decrease in hip structural geometry, and changes in body composition compared to women not reporting arthritis. Compared to the non-arthritic control group, the RA group had a significant 50%, 2-fold, and 3-fold increase in any, spine, and hip fracture risk. When glucocorticoids were taken out of the RA definition and adjusted for as a covariate, fracture risk for any fracture and hip fractures in the RA group remained about the same; however, the increase in spine fracture risk was no longer statistically significant.

In the hip structure analysis, over the study period, the probable RA group had on average a significantly smaller mean hip BMD, outer diameter, cross-sectional area, and section modulus at the femoral narrow neck, indicating decreased hip strength than the non-arthritic control group. Though not statistically significant, the mean buckling ratio was higher in the probable RA group than the control group, again suggesting a reduction in strength. In terms of body composition, the probable RA group had on average 2.3 less percent lean soft tissue mass and 2.4 greater percent fat mass than the non-arthritic control group in addition to significant less absolute lean and significantly more absolute fat mass.

Bone strength, the primary contributor to fracture risk, is comprised of the material and structural properties of the bone. The findings of these studies suggest that declines in hip strength via structural geometry may contribute to the increases in fracture

risk in this population. Body composition is also associated with both the material and structural components of bone strength, and the findings from these studies suggest that body composition is also a factor in bone strength, which is associated with fracture risk in this population.

Bone erosions and joint damage are serious outcomes of RA, and it is possible that joint damage can alter the structural geometry, especially at the femoral neck of the hip, reducing strength. Joint damage is also associated with pain, and limitations in physical activity due to painful joints may lead to alterations in body composition. Inflammation is a key factor is joint damage, and is the primary hypothesized mechanism behind each of the associations found in this dissertation. As indicated by the causal diagram in Figure 5, inflammation, as a consequence of RA, affects body composition and bone strength, which both influence facture risk.

The relationship between inflammation and each of the outcomes has been discussed in previous chapters, but to summarize pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 have been shown to upregulate osteoclastic bone resporption, and can suppress the molecular factors needed to differenetiate mesenchymal stem cells to osteoblasts instead of adipocytes. Pro-inflammatory cytokines also block the anabolic factors, such as IGF-1, needed to mature skeletal muscles cells for muscle growth. In each case, reducing inflammation has been suggested as an avenue to benefit bone strength and body composition. Studies on agents that reduce inflammation in RA have not shown large gains in bone mass, and few studies have assessed how reducing inflammation effects body composition.

Effect of Reducing Inflammation on Bone Strength

There are many biologic agents designed to reduce inflammation in RA with the most widely used being the anti-TNF agents of etanercept, infliximab, golimumab, certolizumab, and adulimumab. The effects of anti-TNF treatment on BMD has been studied, and though one study found a 13% increase in femoral neck and a 3% increase in lumbar spine BMD in RA patients treated with infliximab (170), most of the studies show little to no change in BMD of the RA patients. In a small study of RA patients on adulimumab therapy, a 0.3% increase in both lumbar spine and femoral neck BMD was found after one year after treatment (171). Similarly, other studies have found little to no change in BMD at the either the lumbar spine or the femoral neck after treatment with adulimumab, infliximab, or etanercept (172-174). As indicated in a review by Barnabe and Hanley, the anti-TNF effects on BMD were measured after a relatively short treatment time, which may be the reason why no effect was shown in the marjority of the studies; greater benefit may also be present for RA patients with long-term use of these agents (175). It is also possible, that for high risk patients, like women with RA, inflammation reducing agents such as the anti-TNFs, may reduce the accelerate loss in bone strength , which is ultimately beneficial for overall fracture risk reduction.

Recently, denosumab, a receptor activator of nuclear factor (NF)-κB ligand (RANK-L) monoclonal antibody, has been approved by the FDA to treatment of osteoporosis in postmenopausal women (176). Reductions in bone mass are a result of increased bone resorption by osteoclasts (177), and osteoclast function is regulated by

RANK and RANK-L. Osteoprotegerin (OPG) blocks the action of RANK-L, and the expression of RANK-L/OPG is the determining factor in the occurrence of osteoclast-mediated bone resorption (72). In the phase 3 study of almost 8,000 postmenopausal women, denosumab treatment resulted in a relative 68% reduction in vertebral and a relative 20% reduction in non-vertebral fractures (178).

Denosumab has also been studied in RA patients, as pro-inflammatory cytokines over expressed in RA contribute to the destruction of bone and cartilage by either disrupting RANKL/OPG expression or acting on osteoclasts or pre-cursor cells specifically (Table 26). Cohen et al. found decreases in markers of bone turnover over the treatment period, and also found that over 12 months the BMD improved by 4%, 1.7%, 2.1%, and 1.6% at the lumbar spine, total hip, trochanter, and femoral neck respectively (179). In a follow-up study, the BMD benefits of denosumab were seen irrespective of glucocorticoid and bisphosphonate use in the RA patients (180). These findings suggest that reducing RANK-L and related inflammation, reduces bone resorption by osteoclasts and benefits bone mass in RA patients.

In terms of the structural aspect of bone strength, there have not been any studies exclusively studying the effect of DMARDs, anti-TNF, or newly designed inflammation reducing therapies on hip structural geometry in RA. In non-RA populations, the effect of denosumab in comparison to alendronate, was studied on hip strength using the HSA measurements. The study found that both alendronate and denosumab improved the strength measures at 12 and 24 months, but found that the effects of denosumab were

greater at the itertrochanteric and shaft regions (181). With the inclusion of HSA on the new Hologic software, examination of treatment effects on hip geometry are possible.

Effect of Reducing Inflammation on Body Composition

The effects of inflammation on body composition described in Chapter 8, again suggests that a reduction in inflammation can reduce or prevent the negative body composition changes experience by RA patients; however, there have not been many studies examining the effect of inflammation reduction by DMARDs or anti-TNF agents on body composition. In a study of 19 RA patients using infliximab, no significant changes in DXA-derived lean mass or fat mass were observed after one year of treatment and after adjusting for factors such as age and disease duration (182). In another small study of 20 British RA patients on etanercept, infliximab, and adalimumab anti-TNF therapy, a slight increase in BIA-derived fat free mass and a decrease in body fat was found, however, these differences were not statistically significantly different between baseline and the 12-week follow up (183). The authors did find a significant increase in trunk fat over the 12 weeks, but noted that BIA is limited in measuring regional body fat (183). The RA patients in this study also had an average of 17 years of disease duration, potentially making it difficulty to find any association with ant-TNF therapy and body composition in a short period of time given the advanced disease.

The last study in the literature on anti-TNF therapy and body composition was a 24-week randomized controlled trial comparing body composition outcomes on etanercept versus methotrexate therapy in early RA patients (184). The study did not find

any significant differences in body composition between the two groups over the study period (184). A sub-sample of the patients were followed for 6 months, and though there were no differences in the amount of weight gained between the two groups, those who gained greater than 3% of their baseline body weight in the etanercept group gained a higher percentage of lean mass, whereas there was a higher percentage of fat mass gained in the methotrexate group (184). This suggests that anti-TNF therapy may contribute to the prevention of inflammation-induced increases in fat mass. Longitudinal studies with adjustment of variables related to body composition (ie. exercise and co-morbidities) are needed to better address how reducing inflammation effects body composition.

The Relationship between Body Composition and Bone

In Figure 5, body composition is portrayed as one of the causal pathways linking inflammation to decreasing bone strength. Body composition can also be viewed as a confounder in the inflammation to bone strength association, since composition, primarily fat mass, influences the level of certain inflammatory markers. The studies of this dissertation were not able to determine the exact role of body composition in bone strength in this population, but did show that RA alters body composition, suggesting that maintenance of a health body composition in postmenopausal women with RA may benefit bone strength.

This dissertation was also not able to determine which compartment (lean or fat) of body composition is the most important for bone health in women with RA. If lean is more important for bone strength, then interventions specifically focused on increasing

muscle mass and strength would be needed. If fat mass is more important, then physical and nutritional interventions would be needed to determine the optimal amount of fat needed to produce mechanical stimulation and hormone expression without experience the negative effects of fat mass on other systems of the body.

The research community has not reached a consensus, but a mini review by Reid provided evidence that fat mass is a bigger determinant of BMD in post-menopausal women and pre-menopausal women not participating in regular physical activity (185). Though all women lose bone mass after menopause, estrogen, a major hormone in bone health, is released from adipose tissue, and may prevent the severe decreases in bone mass in those women with more adipose tissue. Specifically in RA, significant correlations with lean mass and BMD have been found (186), but no studies could be found assessing if lean or fat mass is the bigger determinant of BMD.

In Crohn's disease, another inflammatory autoimmune disease, body composition determinants of BMD were examined, and researchers found that only lean mass was significantly positively correlated with BMD (187). When lean and fat mass were in the same model, Lee and colleagues again found an independent association with lean mass and not fat mass, suggesting that lean was a stronger predictor of BMD in Crohn's patients. Preliminary analyses in the WHI-BMD cohort found that both baseline total body lean and total body fat mass were independently associated with baseline BMD. After adjusting for age and weight, increases in lean mass were associated with increases in BMD, and increases is fat mass were associated with decreases in BMD in both women with RA and without arthritis. Similar to the findings of Lee, when lean and fat

mass were combined in the same model, lean mass was the only significant predictor of BMD after adjustment for age in both women with RA and without arthritis (Table 27). With less lean mass and more fat mass than the non-arthritic controls, and the added adipose tissue in RA may contribute to a constant pro-inflammatory feedback from and to the joints, further contributing to the negative effects the pro-inflammatory cytokines have on bone resorption. Though preliminary, the above findings suggest that increasing lean mass, through exercise and strength training, would not only increase muscle mass and strength, which would add to the mechanical strain on bone, but it could also potentially reduce adipose tissue and inflammation, providing more benefit to bone health.

The role of body composition in hip geometry was also not examined in this these studies. As previously mentioned, Travison and colleagues showed that lean mass was a bigger determinant of hip strength (50), and Beck and colleagues found that obesity was associated with a reduction in hip strength (51). It is not known how body composition affect hip structural geometry in RA, but given that lean mass seems to be a bigger determinant of BMD in RA, lean mass may also add to the structural properties of the hip, increasing the overall strength. Ultimately, reducing fracture outcomes in RA is the goal of this research, and studies with a larger RA sample size, with measures of BMD, hip geometry, and body composition are needed to advance the field.

INTERESTING FINDINGS

There were many interesting findings from these analysis. First, was the high prevalence of reports of RA in the WHI. Overall, 5.3% of the women in the WHI-BMD reported RA. This prevalence is higher than expected, but in a cohort of older women, it was not out of the realm of possibility. However, only 14% of the self-reported RA cases were validated with medication, resulting in a lower prevalence of RA than expected. There are several possibilities explaining the over reporting of RA. First, the word rheumatism was historically used to describe conditions affecting the bones, joints, and tendons(188), and it is possible that someone who was told by their physician that they have some sort of rheumatism could mistake it for rheumatoid arthritis.

Secondly, the baseline arthritis questions on the WHI health questionnaire were not properly worded to explore the diagnosis of RA more thoroughly. As previously indicated, if a woman reported having arthritis, her choices for type included "rheumatoid arthritis" or "other/do not know". Women may have selected RA because of the "arthritis" term if they had an arthritic condition, especially given that the other choice was a combination or other and do not know. The WHI changed the wording on follow-up questions to identify RA and OA more specifically, however, only baseline answers were used to define the arthritis groups for these studies.

The baseline characteristics were examined between the arthritis groups (no arthritis, OA, self-reported RA, probable RA) to see if the self-reported RA group had similar characteristics to either the OA or probable RA group. The race/ethnicity distribution and reports of physical activity were more similar between the self-reported

and probable RA groups than the other two groups, but the self-reported RA group was more similar to the OA group in terms of age, smoking, hormone use, weight, BMI, and physical function. These findings suggest that the inclusion of the self-reported RA cases into the RA group would add additional bias to the findings of these studies.

The second interesting finding from these studies was the high proportion of African Americans reporting RA. The percentage of African Americans in the probable RA in the WHI-BMD was nearly 30%. RA is a condition with a higher prevalence in Caucasian populations, so this proportion in the African American population was higher than expected. Birmingham, Alabama, one of the BMD centers, also served as a minority recruitment center, which could explain the larger number of African Americans in the BMD cohort relative to the entire WHI; however, this does not explain the large number of African Americans with RA. Systemic lupus erythematosus (SLE), another rheumatologic condition, is more prevalent in African Americans, so it is possible that some of the women reported having RA instead of SLE (which was a separate question on the WHI baseline health questionnaire), or that a portion of the African American women with SLE were misdiagnosed with RA.

Though there was a large percentage, the overall sample size of the probable RA group was small, resulting in an even smaller number of African Americans in the probable RA group. With such as small sample size in the RA group, there were not enough people to truly examine differences or modifications in the outcomes by ethnicity. Non statistically significant trends were present, but no conclusions could be

drawn that RA affects African Americans differently in terms of osteoporosis related outcomes than their White counterparts.

Overall Strengths and Limitations

The primary limitation of each of the studies is the classification of RA within the WHI. The medication validation of self-reported RA was relatively low, potentially resulting in a fair amount of misclassification in the arthritis exposure groups. The WHI was also not designed to be an arthritis specific study, so important factors such as disease severity and disease duration were not able to be adjusted for or examined as potential modifiers in the studies. Limitations for each the ascertainment of fractures, hip structural geometry, and body composition were described in the corresponding chapters, however, they would affect the entire population and not the RA group differentially.

There are several strengths to these studies. Currently, there are no studies assessing hip structural geometry in RA patients, making this the first study. The findings show that RA not only is associated with reduced BMD, but also various geometric and strength variables. This is also one of the few studies examining body composition longitudinally in RA, and also one of the first studies examining fracture outcomes and body composition in a multi racial and ethnic cohort of RA patients. Cauley and colleagues showed that clinical risk factors for osteoporotic fractures differ by race and ethnicity (25), which makes it important to racial and ethnic differences in studies examining osteoporosis and fracture risk factors. Though limited in potential RA covariates, the study was conducted in Women's Health Initiative, which had information

on most covariates related to fractures, BMD, and body composition. Though the probable RA sample size was small, the overall size of the WHI, allowed for the inclusion of key covariates and the use of more powerful statistical techniques. The findings from these studies can pave the way for future RA studies within the WHI and more sophisticated examination of interplay between body composition and bone strength is RA specific cohorts.

Future Directions

One of the main questions the findings of these studies leads to is how the inclusion of hip geometry improves hip fracture prediction in RA patients. As mentioned in chapter 8, there were only four hip fractures in the probable RA group of the WHI-BMD, and with the small number of fractures, analysis like those conducted by LaCroix and colleagues in the WHI-BMD could not be performed. Another important next question, is how body composition affects bone strength in RA. This and other previous studies show RA is related to a decrease in bone strength and that RA alters body composition, but there have not been an studies putting the two together. Additional studies with longer follow-up of anti-TNFs should be performed to gauge the effect on reducing inflammation on BMD and body composition.

In the WHI, there is currently a project conducting molecular validation of the RA cases including the presence of rheumatoid factor and anti-cyclic citrullinated peptide antibodies. More definitive classification of the RA using these biomarkers will assist the RA research within the WHI. Once the validation is complete, it will be interesting to see

how the fracture, hip geometry, and body composition results using the molecular validated cases compares to the medication validation cases. It will also be interested to see if the racial and ethnic differences are still present within the RA group with the molecular validation. The molecular validation could potentially capture those RA cases not reporting medication, increasing the sample size to continue these studies within the WHI.

CONCLUSIONS

These studies provide evidence of the negative effects of RA on bone strength and body composition, two important aspects in fracture risk. The long-term goal of this dissertation was to better understand the mechanisms of bone loss in postmenopausal women with RA, in order to target preventative approaches for reducing bone loss and fracture risk. Based on this dissertation, clinical examination of bone strength and body composition, in addition to the control of inflammation, will not only reduce disease activity, but also aid in the prevention of fractures in RA.

Table 26: The Effect of Cytokines and Factors Associated with RA on Osteoclasts

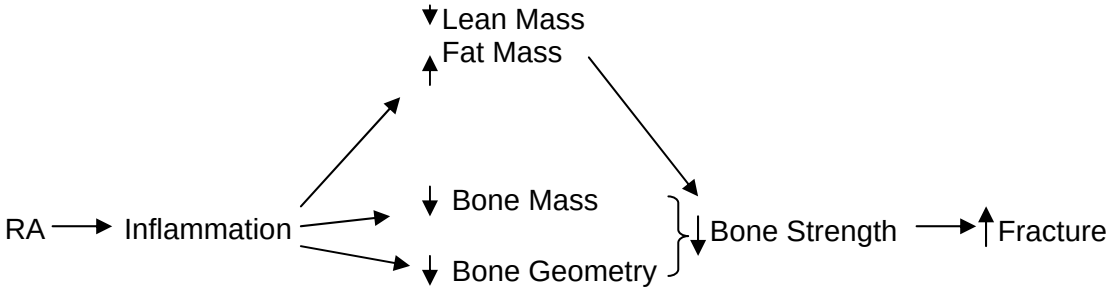
Factor	Sources	Function
Interleukin-1 (IL-1)	• Produced by macrophages, monocytes and dendritic cells • Expressed by osteoclasts • Two types: IL-1α & IL-1β	• Stimulate osteoclastic bone resorption • Affects all stages in osteoclast differentiation, but primarily the early stages
IL-6	• No definitive source of synthesis • Generated in bone in response to PTH, IL-1 & TNF	• Indirect effect on osteoclasts cells • Enhances the effects of other cytokines and systemic hormones on bone resporption • Resorption effects are enhanced by soluble IL-6 receptor
TNF-α	• Macrophages	• Stimulates osteoclast bone resorption • Causes increases in blood Ca2+ levels
Monocyte-Macrophage Colony Stimulating Factor	• Osteoblasts and bone lining cells, T-cells	• Direct effect on activity of osteoclasts

Table 27: Effect of Body Composition on BMD by Arthritis Status

	No Arthritis n = 5067				Probable RA n = 82			
	Coef.	**SE**	**p-value**	**R2**	**Coef.**	**SE**	**p-value**	**R2**
Model 1				0.2317				0.1188
Total Body LSTM	0.0061	0.0004	<0.001		0.0096	0.0037	0.011	
Age	-0.0041	0.0002	<0.001		-0.0020	0.0018	0.256	
Weight	0.0002	0.0001	0.156		-0.0010	0.0013	0.446	
Model 2				0.1958				0.1764
Total Body FM	-0.0017	0.0003	<0.001		-0.0109	0.0031	0.001	
Age	-0.0044	0.0002	<0.001		-0.0019	0.0017	0.267	
Weight	0.0027	0.0002	<0.001		0.0093	0.0023	<0.001	
Model 3				0.2312				0.1293
Total Body LSTM	0.0065	0.0003	<0.001		0.0092	0.0027	0.001	
Total Body FM	0.0000	0.0001	0.876		-0.0016	0.0013	0.219	
Age	-0.0041	0.0002	<0.001		-0.0022	0.0018	0.215	

LSTM = lean soft tissue mass; FM = fat mass

Figure 6: Theoretical Framework of the Association between RA and Fractures



APPENDIX A

Description and Frequency of WHI Questionnaires

Frequency of Data Collection

		Screening CT and OS				CT																				OS			
Form #	Form Name	SV 0	SV 1	SV 2	SV 3	4-6 wk	6 m	**1 Yr**	4 wk	6 m	**2 Yr**	6 m	**3 Yr**	6 m	**4 Yr**	6 m	**5 Yr**	6 m	**6 Yr**	6 m	**7 Yr**	6 M	**8 Yr**	6 m	**9 Yr**	Close Out	An-nual	3 Yr	6 Yr	9 Yr
2	Eligibility Screen	X																											
4	HRT Washout		H																										
10	HT Manage/Safety Interview					H	H	H		H	H	H	H	H	H	H	H	H	H	H	H	H	H	H	H				
17	CaD Manage/Safety Interview								C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C				
20	Personal Information		X	X	X																								
25	Participant Treatment Assignment – HT[1]																												
28	Participant Treatment Assignment – CaD																								X				
30	Medical History		X																										
31	Reproductive History			X																									
32	Family History				X																								
33	Medical History Update						X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
34	Personal Habits				X																								
35	Personal Habits Update							X					X						X						X					
37	Thoughts & Feelings			X																					X				
38	Daily Life							X					%						%						%			X		
39	Cognitive Assessment				%H			%H					%H						%H						%H					
40	Addendum to Medical History[1]																												
41	Addendum to Personal Info[1]																												
42	OS Questionnaire[1]			O																									
43	Hormone Use Interview		X																										
44	Current Medications		X					X					X						X						X			X		
45	Current Supplements		X					X					X						X						X			X		
48	OS Follow-Up Questionnaire[1]																												
49	E+P Survey[1]																												
55	E-Alone Survey[1]																												
60	Food Questionnaire		X					D			%D		%D		%D		%D		%D		%D		%D		%D			X		
80	Physical Measures		X					X			X		X		X		X		X		X		X		X			X	BD	
80	Waist/Hip Measures		X					X					%						%						%			X		
81	Pelvic			H				H			H		H		H		H		H		H		H		H					
82	Endometrial Aspiration			H									%H						%H						%H					
83	Transvaginal Uterine Ultrasound[1]																												

		Screening CT and OS				CT																					OS			
Form #	Form Name	SV 0	SV 1	SV 2	SV 3	4-6 wk	6 m	**1 Yr**	4 wk	6 m	**2 Yr**	6 m	**3 Yr**	6 m	**4 Yr**	6 m	**5 Yr**	6 m	**6 Yr**	6 m	**7 Yr**	6 M	**8 Yr**	6 m	**9 Yr**	Close Out	An-nual	3 Yr	6 Yr	9 Yr
84	Clinical Breast Exam			HD				H			H		H		H		H		H		H		H		H					
85	Mammogram			HD				H			X		H		X		H		X		H		X		H	H				
86	ECG			HD									X						X						X					
87	Bone Density		BD					BD					BD						BD						BD	BD		BD	BD	BD
90	Functional Status				%HD			%					%						%						%					
92	Pap			H									H						H						H					
100	Blood Collection		X					X					%						%						%			X		
101	Urine Collection		BD					BD					BD												BD			BD		BD
143	OS Follow-up (Year 3)																											X		
144	OS Follow-up (Year 4)[1]																													
145	OS Follow-up (Year 5)[1]																													
146	OS Follow-up (Year 6)																												X	
147	OS Follow-up (Year 7)[1]																													
148	OS Follow-up (Year 8)[1]																													
149	Supplement to OS Follow-up[1]																													

[1] See description in Baseline and Follow-up Variables table for timing of data collection.

Key: X = All Participants
D = DM
H = HRT
C = CaD
O = OS
% = Percentage (subsample) of participants
BD = Bone Density sites

Baseline and Follow-Up Variables

Form and variables	Timing and Subsample Notes (See table above for frequency of collection)
Form 2 - Eligibility Screen -- name; mailing address; telephone numbers and best times to call; date of birth; residing in area for next three years; current involvement in other research studies; history of cancer (site, diagnosis in past 10 years); ethnicity; recruitment source; hormone use (present, in last three months); osteoporosis-related fracture and hormone use as treatment; hysterectomy history; last menstrual bleeding; number of meals prepared away from home; special diets (type); history of diabetes, deep vein thrombosis, pulmonary embolus, stroke, transient ischemic attack, myocardial infarction; history of sickle cell anemia, heart failure, liver disease, bleeding problem; loss of 15 pounds in last six months; renal failure requiring hemodialysis; other chronic illness; emotional or mental problems; ability to get to clinical center; interest in DM; interest in HRT (willingness to stop current hormone medications).	Updated at final screening contact.
Form 4 - HRT Washout -- date stopped hormones; assessment of symptoms after stopping (HT for those on hormones at initial contact).	
Form 10 - HRT Management and Safety Interview -- presence and amount of vaginal bleeding; changes in breasts; currently taking medications, or have symptoms, worries, or health changes that might require stopping study pills; pill-taking behaviors.	Required semi-annually and at non-routine contracts initiated by participant while HRT participants were taking study pills, and for two semi-annual contacts after stopping study pills.
Form 17 - CaD Management and Safety Interview -- presence of gastrointestinal symptoms, currently taking medications, or have symptoms, concerns, or health changes that might require stopping study pills; pill-taking behaviors.	Required semi-annually and at non-routine contracts initiated by participant while CaD participants were taking study pills, and for one semi-annual contact after stopping study pills.
Form 20 - Personal Information --education; employment status; occupation; marital status; partner's education, employment status, occupation; total family income; recent history of mammogram, pelvic exam, endometrial aspiration; insurance coverage; serve in armed services.	
Form 25 – Participant Treatment Assignment: Estrogen plus Progesterone/E-Alone – date stopped study pills; symptoms when stopped; guess on treatment assignment and reasons.	For E+P, when intervention stopped July 9, 2002. For E-Alone, when intervention stopped in February 2004.
Form 28 – Participant Treatment Assignment CaD -- when stopped study pills, guess on treatment assignment and reasons.	At CaD study close-out October 2004-March 2005.
Form 30 - Medical History Questionnaire -- hospitalization history; history of medical conditions; history of heart, circulatory, or coagulation problems; history of arthritis, gallbladder disease, thyroid disease, hypertension, angina, peripheral arterial disease and related procedures, colonoscopy or sigmoidoscopy, stool guaiac; history of cancers (site, age at diagnosis); recent history of falls or syncopal episodes; history of fractures (site, age, number).	

Form and variables	Timing and Subsample Notes (See table above for frequency of collection)
Form 31 - Reproductive History -- age at menarche; history of menstrual irregularity and amenorrhea; history of menopausal symptoms; history of pregnancy, pregnancy outcomes, infertility; history of breast feeding; history of gynecologic and breast surgeries.	
Form 32 - Family History Questionnaire -- number of full-blooded sisters and brothers, daughters, and sons; parental age or date of death; relatives' history of' diabetes, myocardial infarction, stroke, cancers; fractures in parents (site, age).	
Form 33 - Medical History Update -- hospitalization since last contact; hospitalization for heart, circulatory, or coagulation problems; stroke or transient ischemic attack, number of falls or syncopal episodes, fractures update; cancer (type, where diagnosed, hospitalization); mammogram; breast biopsy, needle aspiration, or lumpectomy; tests and procedures; electrocardiogram; diagnosis of new conditions; hip or other joint replacement.	
Form 34 - Personal Habits Questionnaire -- coffee consumption; smoking history; alcohol history; weight change; special diets; history of physical activity and exercise (frequency, duration).	
Form 35 - Personal Habits Update —physical activity and exercise; alcohol consumption; current cigarette smoking.	
Form 37 - Thoughts and Feelings -- social support; social integration; care giving; social strain; optimism; negative emotional expressiveness; hostility; Form 38 – Daily Life items: quality of life; symptoms; life events; depression; sleep disturbance; urinary incontinence; sexual functioning.	
Form 38 - Daily Life -- quality of life; symptoms; life events; depression; sleep disturbance; urinary incontinence; sexual functioning.	6% CT cohort subsample (8.6% HT and 4.3% DM; same as Form 80 [for hip/waist] and Form 100-Blood cohort).
Form 39 - Cognitive Assessment -- expanded mini mental status examination.	HT cohort aged 65 and over.
Form 40 - Addendum to Medical History Update -- family history of DVT and PE. (2002)	Initiated in 2002 and collected once from all CT and OS participants at next routine contact.
Form 41 - Addendum to Personal Information -- racial/ethnic background using 2000 Census questions. (2002)	Initiated in 2002 and collected once from all CT and OS participants at next routine contact.
Form 42 - Observational Study Questionnaire -- birth weight, birth status, breast feeding at birth; coffee/tea consumption; alcohol history; smoking history; history of breast examination, history of benign breast disease, recent history of mammogram; history of the use of powders in genital area or on sanitary napkins; history of diaphragm; history electric blanket use; religious affiliation; recent history of physical activity and exercise (frequency, duration); occupational history; height and weight history, weight change; state of residence history.	
Form 43 - Hormone Use Interview– current and past hormone replacement (duration, frequency); history of oral contraceptive, diethylstilbestrol, depo-provera use.	

Form and variables	Timing and Subsample Notes (See table above for frequency of collection)
Form 44 – Current Medications –.current medication name, form, strength, duration.	
Form 45 – Current Supplements –.current supplement name; vitamin and mineral type, dose, frequency, duration.	
Form 48 – OS Follow-up Questionnaire (Year 1) -- current weight, recent weight change; current food and beverage consumption at meal or snack times, recent use of fats or oils, recent wine consumption; current smoking habits; recent history of hormone replacement; history of insecticide exposure; history of living with pets; history of computer use (frequency, duration); history of hand-held hair dryer use (frequency, duration).	
Form 49 - Estrogen Plus Progestin Survey – date stopped; take hormones since stopped and reasons; take hormones now; current symptoms and severity; how manage symptoms; depression scale; sexual functioning; current medications, natural hormones; quality of life.	For E+P participants on study through July 8, 2002, when intervention was; administration began in March 2003.
Form 55 - Estrogen-Alone Survey – current symptoms; how manage symptoms; sexual functioning; current medications, natural hormones; take hormones since stopped and reasons; take hormones or SERMS now.	For all E-Alone participants; administered twice: first in Jan. 2004 before the intervention was stopped on February 28, 2004, and again at close-out visit.
Form 60 – Food Questionnaire -- 145 item Food Frequency Questionnaire.	Year 2: 30% cross sectional; Year 3,6: 4.3% cohort (same as blood subsample) and 5.7% repeated cross-sectional; Year 4,5,7: 10% cross-sectional. In 2000 implemented subsample so each DM participant received a FFQ at least once every 3 years.
Form 80 - Physical Measurements – resting pulse and blood pressure; height, weight; waist and hip circumference.	Waist and hip measurements at Year 3,6, and 9 in 6% CT cohort subsample (8.6% HT and 4.3% DM; same as Form 38-Daily Life and Form 100-Blood cohort). For BD sites, height at OS Year 6.
Form 81 - Pelvic Exam – physical exam results; presence of cystocele, rectocele; uterine presence, size, prolapse; adnexae; follow-up results.	Not required for E+P participants after July 9, 2002, when intervention was stopped.
Form 82 - Endometrial Aspiration – uterine depth; aspiration results; follow-up results.	5% E+P participants with uterus at indicated contacts, and at other contacts to manage unexpected bleeding. Not required after July 9, 2002, when intervention was stopped.
Form 83 – Transvaginal Uterine Ultrasound – endometrial thickness; pathology results; endometrial cavity fluid; follow-up results.	Done only if endometrial aspiration could not be done or was refused.

Form and variables	Timing and Subsample Notes (See table above for frequency of collection)
Form 84 - Clinical Breast Exam – nipple discharge; skin, axillary, or breast mass; mass size, mobility, number; follow-up results.	Optional for DM participants.
Form 85 - Mammogram -- summary results, follow-up results.	
Form 86 – ECG – 12 lead ECG	
Form 87 – Bone Density Scan – hip, spine, and whole body scan	Collected only at 3 Bone Density sites; not required on enhanced recruitment participants at these sites. Collected at close-out if did not reach Year 9.
Form 90 - Functional Status -- grip strength; chair stand; 6 meter timed walk.	25% CT cohort aged 65 and over.
Form 92 - Pap Smear -- type cells present; pathology results; follow-up results.	HT women with cervix.
Form 100 - Blood Collection and Processing -- hematocrit, white blood cell count, platelet count, fasting triglycerides (for HT participants if serum lipemic); fasting serum, plasma (citrate and EDTA), buffy coat, RBCs for storage; time since ate; physical exercise and aspirin use before blood drawn; time drawn, centrifuged, removed from cells, frozen.	6% CT cohort subsample (8.6% HT and 4.3% DM; same as Form 38-Daily Life and Form 80 [for hip/waist] cohort). Hct, platelet count, WBC done only at screening on CT and OS participants; triglyceride done on HT participants if serum lipemic.
Form 101 - Urine collection and Processing – first morning void urine for storage; time collected, centrifuged, removed to vials, frozen.	Collected only at 3 Bone Density sites; not required on enhanced recruitment participants.
Form 143 - OS Follow-Up Questionnaire (Year 3) -- recent weight change, figure (weight) identification; current physical activity and exercise (frequency, duration); usual activities; past strenuous physical activity by age (frequency); recent alcohol consumption, change in alcohol consumption habits; recent coffee/tea/water/diet drinks consumption; recent use of fats or oils; current smoking, current smoking exposure; current employment status, current marital status, partner's current employment status; total family income; existence and recent use of usual medical care provider, change in usual medical provider; choice options in current health insurance coverage, type(s) of current health insurance coverage and payment mechanism; recent use of hormone replacement therapy; diagnoses of new medical conditions.	OS Follow-Up Questionnaire not done at Year 2.
Form 144 - OS Follow-Up Questionnaire (Year 4) -- current weight, recent weight change; current physical activity and exercise (frequency, duration); exposure and sensitivity to sunlight; current smoking; past and present use of artificial sweeteners; recent use of hormone replacement therapy; diagnoses of new medical conditions; current marital status.	
Form 145 – OS Follow-Up Questionnaire (Year 5) -- current weight, recent weight change; current physical activity and exercise (frequency, duration); current smoking; video, video display terminal exposure; depression scale; frequency religious practices; recent use of alternative medical treatments; current dental health, frequency of professional dental care; recent use of hormone replacement therapy;	

diagnoses of new medical conditions; current marital status.	
Form and variables	**Timing and Subsample Notes** (See table above for frequency of collection)
Form 146 – OS Follow-Up Questionnaire (Year 6) -- current weight, recent weight change; current physical activity and exercise (frequency, duration); usual activities; coffee, tea, soft drink, alcohol consumption; current smoking; smoking exposure; existence and recent use of medical care provider, status and types of health insurance; use of natural hormones; use of osteoporosis prescription medications; recent use of hormone replacement therapy; diagnoses of new medical conditions; family history of Alzheimer's; current employment status; current marital status; family finances.	
Form 147 – OS Follow-Up Questionnaire (Year 7) -- current weight; recent weight change; current physical activity and exercise (frequency, duration); use of weight loss medications; recent use of hormone replacement therapy; diagnoses of new medical conditions; family history of breast cancer; life events; parents' birthplace; current marital status.	
Form 148 – OS Follow-Up Questionnaire (Year 8) -- current weight; recent weight change; current physical activity and exercise (frequency, duration); current smoking status; use of weight loss medications; coffee, tea, soft drink consumption ; recent use SERMS, recent use of hormone replacement therapy; diagnoses of new medical conditions; family history of senile dementia; current marital status.	
Form 149 – Supplement to OS Follow-Up Questionnaire (Year 9) -- care giving responsibilities; life events; breast cancer; use of weight loss medications; parents' birthplace.	For OS participants who did not reach Year 7 by time of closeout.

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