Bone Functional Adaptation: Life History Constraints and Implications for Aging Research

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Abstract

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This dissertation examines skeletal adaptation across human life history, emphasizing how reproductive investment and aging influence bone mineral density (BMD), a crucial determinant of bone health and resilience. Specifically, it investigates how parity, habitual mechanical loading, and cellular aging–proxied by leukocyte telomere length (TL)--interact to shape regional variation in BMD. The first study analyzed associations between parity and regional BMD using anthropometric, dual-energy X-ray absorptiometry, health biomarker, and questionnaire data from the National Health and Nutrition Examination Survey (NHANES cohorts 2007–2018). Results showed that higher parity was linked with lower BMD, particularly in metabolically active skeletal sites such as the lumbar spine, highlighting the metabolic demands of reproduction on skeletal maintenance. The second study assessed whether habitual

mechanical loading could buffer age-related BMD loss by comparing weight-bearing and non-weight-bearing skeletal regions. Findings demonstrated similar age-related declines between weight-bearing and non-weight-bearing regions, though gendered differences emerged; women experienced steeper declines in non-weight-bearing regions compared to weight-bearing regions, indicating that loading alone is insufficient to protect against aging-related skeletal deterioration. The third study investigated whether telomere length, a biomarker of cellular aging, is associated with regional BMD variation and parity (NHANES 1999–2002). Results showed that shorter TL correlated with lower BMD selectively in women but did not mediate the association between parity and BMD. Together, these findings demonstrate that reproductive history and cellular aging independently influence skeletal health across the lifespan. This dissertation emphasizes the complexity of skeletal aging and the importance of integrating life history theory, biomechanical analysis, and cellular biology to understand bone health in evolutionary, clinical, and public health contexts.

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DEDICATION

For my mother, Eva, who once told me that the single most important thing I could do as a woman was to pursue an education.

Chapter 1. INTRODUCTION

Bone remodeling and, consequently, bone health are crucial determinants of individual healthfulness over the life course, influencing mobility, morbidity, and mortality risk as humans age. Bone is an extraordinarily sensitive tissue, continuously changing through evolutionarily conserved processes that involve complex cellular interactions, hormonal regulation, and mechanical stimuli. Understanding this process provides essential insights into broader patterns of human health, aging, and evolutionary biology. This dissertation investigates these processes by exploring parity, age-related variation in bone mineral density (BMD), and molecular biomarkers of aging, such as telomere length, by analyzing data derived from the National Health and Nutrition Examination Survey (NHANES).

The overarching questions addressed in this work center on bone remodeling and its responses to evolutionarily relevant events or circumstances, specifically, reproductive investment and aging. By examining these responses as a form of somatic maintenance, this dissertation aims to contribute to theoretical and clinical understandings of bone remodeling and its influence on human adaptation, health outcomes, and disease prevention strategies, specifically concerning osteoporosis and fracture risks.

Life history theory provides a framework for understanding the consequences of allocating limited energetic resources to growth, maintenance, and reproduction across the human life course. Through this lens, bone's form and function are more than structural elements that simply provide a mechanical scaffold for movement; they are integral to human evolutionary trade-offs. Evolutionary fitness demands successful reproduction, which incurs energetic costs. For humans, reproductive events, particularly pregnancy, parturition, lactation, and the

obligatory intensive care of altricial offspring, impose substantial metabolic and biomechanical demands on the maternal body. These demands are hypothesized to drive trade-offs in somatic maintenance, including bone maintenance, potentially influencing how bone remodeling is regulated across the lifespan (Jasienska, 2009, 2020a; Nilsson & Svenssonn, 1996; Ziomkiewicz et al., 2016). An evolutionary and life-history lens can help contextualize interactions between the demands of resource-limited energy allocation, reproductive costs, and aging processes, framing bone pathologies (e.g., osteoporosis) not solely as a disease of modernity but as a downstream consequence of fundamental adaptive strategies (Madimenos, 2015a).

The dissertation is structured as a multi-chapter thesis. Chapter 4 presents an in-depth analysis of the association between parity and BMD among U.S. living women using NHANES data. This chapter applies human reproductive cost and life history theories to explore whether reproduction (proxied by parity, or number of births) has enduring effects on BMD and, if they exist, whether such effects vary by anatomical region. This chapter examines reproduction as a potential source of both physiological strain and mechanical loading, evaluating region-specific BMD outcomes to assess whether skeletal regions more regularly exposed to relatively higher ground reaction forces (e.g., femoral neck and lumbar spine) are variably impacted by parity compared to less regularly loaded sites (e.g., ribs and arms).

Chapter 5 expands the analysis beyond parity to consider broader demographic and lifestyle patterns in BMD variation with age. Drawing on a larger NHANES sample, this chapter compares BMD and its age-related decline between weight-bearing and non-weight-bearing skeletal regions to investigate whether mechanical loading buffers more regularly loaded skeletal regions against BMD loss with age. It demonstrates that while mechanical loading plays a role in mitigating bone loss, the impact of aging on BMD remains substantial across all anatomical

regions. Notably, the chapter highlights the effect of demographic and lifestyle factors (e.g., racialized grouping, socioeconomic status, and behaviors like smoking) on bone aging outcomes. The results of Chapter 5 demonstrate the complex nature of BMD regulation and emphasize that mechanical loading, though essential, does not act in isolation.

Chapter 6 aims to better understand the biological mechanisms underlying these findings by investigating telomere length, a biomarker of cellular aging, and its association with BMD. This chapter integrates insights from the previous two chapters and molecular aging research to hypothesize pathways that link cellular senescence to BMD decline. It builds upon the causal model that telomere attrition, DNA damage at the ends of chromosomes that contributes to cellular senescence and age-related diseases mediate or moderate the relationship between bone remodeling, age, and reproduction. The chapter concludes with a discussion emphasizing the importance of future research to utilize longitudinal data, comprehensive and cross-cultural reproductive histories, and in-depth assessments of bone microarchitecture to better understand how cellular mechanisms influence reproduction-related life history tradeoffs.

Together, these chapters provide a novel approach to understanding variation in forensic, archeological, and orthopeadic research findings that rely on hominin osteological remains to infer behavioral, life history, and reproductive trade-offs. This dissertation offers a nuanced investigation of bone maintenance across the life course by leveraging a nationally representative data set and situating analyses within an evolutionary framework. It bridges anthropological theory, epidemiological methodology, and clinical relevance to advance our understanding of osteoporosis, aging, and the embodied costs of reproduction.

Chapter 2. BACKGROUND

2.1 Bone Structure and Physiological Function

Bone is a dynamic and mechanically responsive tissue that plays several critical roles in human physiology, from providing structural support to serving as a mineral reservoir to be drawn upon in times of nutritional scarcity or immunological response (Eriksen, 2010a; Hadjidakis & Androulakis, 2006). Far from inert scaffolding, bone is continuously metabolically active and remodels itself throughout the lifespan, allowing it to adapt to environmental and biological pressures. The adult human skeleton consists of approximately 206 bones, each a composite of organic and inorganic components that must balance strength and flexibility to resist excessive deformation during exposure to ground reaction forces as humans navigate their environments (Ruff et al., 2006). Bone provides structural integrity, serving as a rigid framework to support the body and protect vulnerable organs such as the brain, heart, and lungs from mechanical trauma. Structurally, bone tissue is organized into two key forms: cortical bone, the dense, compact outer shell that provides strength and rigidity, and trabecular bone, the porous, lattice-like network found mainly at the ends of long bones and in vertebral bodies. Together, these forms support three critical functions: structural integrity and protection, hematopoiesis, and mineral storage (Ruff et al., 2006).

Bone's exceptional material properties cannot be overstated. Its strength and adaptability are the result of its composite nature: an inorganic mineral phase made primarily of hydroxyapatite (a crystallized form of calcium phosphate) and an organic matrix made of type I collagen. The mineral component provides rigidity and resistance to compression, while the collagen matrix offers tensile strength and elasticity, allowing bones to absorb and distribute mechanical loads efficiently (Frost, 2003a; Hadjidakis & Androulakis, 2006). Cortical bone,

found primarily in the shafts of long bones, makes up roughly 80% of total adult bone mass. Its dense and highly organized structure provides strength and stability, essential for weight-bearing and locomotion (Bayraktar et al., 2004).

Trabecular bone, however, constitutes about 20% of skeletal mass and is found mainly in areas requiring shock absorption and flexibility. Its spongy, lattice-like structure allows it to absorb and dissipate mechanical forces efficiently, and its high surface-area-to-volume ratio contributes to its relatively higher remodeling rates and greater responsiveness to hormonal and mechanical signals (Bayraktar et al., 2004; Chirchir et al., 2015; Oftadeh et al., 2015). A tightly regulated coordination between cellular specialization, vascular support, and mechanical sensing underscores bone's remarkable capacity to remain both structurally resilient and biologically responsive throughout life (Hadjidakis & Androulakis, 2006).

Beyond mechanical function, bone is also central to critical metabolic and hematopoietic functions. Bone also functions as a mineral reservoir, containing roughly 97% of the body's calcium and 85% of its phosphorus. These minerals can be mobilized during nutritional stress or physiological demands, such as during pregnancy, lactation, or periods of nutritional scarcity (Hadjidakis & Androulakis, 2006; Seibel, 2002). The maintenance of blood calcium homeostasis is crucial for many physiological processes, including nerve transmission, muscle contraction, and blood coagulation. This mineral mobilization is mediated by osteoclasts, or bone-resorbing cells derived from hematopoietic precursors (Shaker & Deftos, 2023; Zhu & Prince, 2012).

Further, bone tissue serves as an endocrine organ, secreting hormones like osteocalcin, which influences glucose and lipid metabolism, insulin sensitivity, and testosterone production(Fukumoto & Martin, 2009). Finally, but importantly, bone houses the marrow cavity, a primary site for hematopoiesis. Bone marrow, housed in trabecular spaces, generates

hematopoietic stem cells, which further differentiate into erythrocytes, leukocytes, and platelets and are essential for oxygen transport, immune function, and hemostasis, respectively. With aging, red marrow gradually transitions to predominantly fatty yellow marrow but remains an important location for maintaining immune function (Tsukasaki & Takayanagi, 2019).

Bone's functional versatility is reliant on a series of specialized cells: osteoblasts, osteoclasts, and osteocytes, which coordinate to facilitate continuous bone remodeling throughout an individual's life. Osteoblasts are responsible for new bone formation, synthesizing collagen matrix, and regulating mineralization. These cells originate from mesenchymal stem cells and can transform into osteocytes once embedded within the bone matrix (Hadjidakis & Androulakis, 2006). Osteocytes, housed within tiny spaces known as lacunae, communicate extensively through a complex network of canaliculi. They are vital mechanosensors, detecting mechanical stress and orchestrating appropriate bone remodeling responses to adapt the skeleton to habitual loading patterns (Aarden et al., 1994; Dallas & Bonewald, 2010).

2.2 Bone Growth and Developmental Modeling

Bone growth and developmental modeling are critical stages in the formation and maturation of the skeletal system, occurring primarily during fetal development and extending through adolescence into early adulthood. These processes are responsible for shaping the skeleton determining bone size, shape, and peak mechanical strength(White et al., 2011).

Early life bone formation begins *in utero* through two primary ossification mechanisms: endochondral ossification and intramembranous ossification. Endochondral ossification, responsible for forming long bones such as the femur, humerus, and tibia, begins with a cartilage template produced by specialized cells known as chondrocytes. Chondrocytes proliferate and

create a dense cartilage matrix, which eventually hypertrophies and calcifies the surrounding matrix, preparing it for bone formation. Blood vessels invade this calcified cartilage, delivering osteoprogenitor cells that differentiate into osteoblasts, the builders of bone tissue (Gilbert, 2000; Hadjidakis & Androulakis, 2006; White et al., 2011).

Intramembranous ossification, however, directly forms bone without an intermediary cartilage phase. It primarily shapes flat bones, such as those found in the skull, and some irregular bones, like the clavicle. During intramembranous ossification, mesenchymal stem cells cluster together and differentiate directly into osteoblasts, which then produce osteoid, or unmineralized bone matrix. Over time, osteoid fully mineralizes to form mature bone, creating flat bones characterized by thin layers of cortical bone surrounding thin trabecular centers (Fernández-Iglesias et al., 2021; White et al., 2011).

Bone length is driven by longitudinal expansion at epiphyseal growth plates, which are systematically organized into distinct zones: resting, proliferative, hypertrophic, and calcified. Chondrocytes in the proliferative zone rapidly divide, adding new cells that elongate the bone, while hypertrophic chondrocytes enlarge and facilitate matrix calcification, eventually replaced by fully ossified bone. This process continues through adolescence until early adulthood when growth plates fuse, marking the completion of linear growth with distal regions of the skeleton fully ossifying before proximal regions. (Ambrosi et al., 2021; Fernández-Iglesias et al., 2021; White et al., 2011)

Throughout bones' developmental period, the growth rate at the epiphyseal plates is regulated by systemic hormones, nutritional status, and mechanical forces. Human growth hormone (HGH), insulin-like growth factor-1 (IGF-1), and sex hormones (e.g., estrogen and testosterone) play key roles in modulating bone elongation and maturation (Fernández-Iglesias et

al., 2021; Gilbert, 2000; White et al., 2011). Estrogen, for example, is essential for the eventual closure of growth plates during late adolescence, marking the end of linear skeletal growth. This hormonal regulation maintains the tight coordination between bone growth and developmental timelines in humans(Khosla et al., 2012; Popat et al., 2009).

Bone modeling, distinct from bone remodeling, refers to the independent processes of bone formation and resorption that shape the skeletal architecture during growth. Modeling enables significant changes in bone shape, size, and geometry, responding to mechanical stresses and optimizing bone structure for functional demands (Gunter et al., 2012; Pate et al., 2012). Unlike remodeling, where osteoclast and osteoblast activities are coupled at the same site, modeling involves uncoupled and distinct regions of bone formation and resorption (Hadjidakis & Androulakis, 2006). For instance, during the rapid skeletal growth of adolescence, periosteal bone deposition (bone formation on the outer surface) occurs simultaneously with endosteal resorption (bone removal from the inner surface), resulting in bones that are larger, thicker, and more capable of withstanding mechanical loads(Gunter et al., 2012; White et al., 2011).

Mechanical forces significantly influence bone modeling during growth because regular physical activity and skeletal loading promote osteoblast activity, increasing bone deposition growth. Reduced mechanical loading, however, or its absence (e.g., sedentary lifestyles or prolonged immobilization) suppresses osteogenesis, potentially leading to low bone mass and poorly assembled microarchitecture. Thus, childhood and adolescent physical activity levels critically impact peak bone mass and skeletal strength, affecting lifelong fracture risk and skeletal integrity (Eriksen, 2010a; Frost, 2003a; Gilbert, 2000; Gunter et al., 2012; Lian et al., 2011a).

Adequate nutrition, particularly calcium, phosphorus, vitamin D, and protein, is critical to producing the materials required for bone tissue formation (Boot et al., 1997). Calcium and phosphorus are fundamental components of hydroxyapatite (Zhu & Prince, 2012); vitamin D promotes calcium absorption within the gastrointestinal tract and regulates bone mineralization, while protein provides the necessary amino acids for collagen synthesis(Shams-White et al., 2017). Deficiencies during critical growth periods can compromise bone mineral density, growth velocity, and final adult bone mass (Rizzoli, 2008; White et al., 2011).

Further, genetic factors significantly influence bone growth and modeling processes. Genetic variation associated with growth factors, hormone receptors, and extracellular matrix proteins may alter growth trajectories, impacting bone length, mass, and the risk of several skeletal disorders (Gilbert, 2000; Wallace, Demes, et al., 2017). Genetic determinants also interact with environmental influences (Rubio-Gutierrez et al., 2022), including physical activity (Wallace, Demes, et al., 2017), nutritional status(Zhu & Prince, 2012), and pollutant exposures, to shape individual variation in skeletal morphology, BMD, and strength.

2.3 Peak Bone Mass and Early Life Influences

Roughly 80-90% of peak bone mass (PBM) is acquired in the first two decades of life, with the remainder accumulating into the third decade(Weaver et al., 2016). PBM serves as an important determinant for lifelong skeletal health, profoundly influencing an individual's susceptibility to osteoporosis and fractures in later life. Achieving optimal bone mass accrual during early life establishes the maximum protective buffer against inevitable bone loss associated with aging (Berger et al., 2010). Longitudinal and twin studies estimate that 60–80% of individual variation in PBM is genetically determined, reflecting differences in bone cell

activity, hormonal responsiveness, mineral metabolism, and growth factor expression(Arden et al., 1996; Berger et al., 2010; Dequeker et al., 1987) Recent evidence further reinforces this connection by showing that higher PBM not only predicts higher BMD in adulthood but also delays the onset of clinically significant bone loss (Berger et al., 2010; Weaver et al., 2016).

Further, individual age at PBM varies, although females typically reach it earlier than males. Sex hormones, primarily estrogen and testosterone, substantially influence bone development during puberty and are responsible for driving bone growth, sexual dimorphism in skeletal traits, and regulating epiphyseal fusion. Dysregulation or delay in pubertal hormone secretion can impair PBM attainment, increasing long-term skeletal vulnerability to adverse aging outcomes (Berger et al., 2010; Orwoll et al., 2001). Estrogen, in particular, promotes osteoblast-mediated bone formation and inhibits osteoclast activity, while also mediating growth plate closure (Khosla et al., 2012). Testosterone enhances bone accrual through periosteal expansion, contributing to greater skeletal mass in males (White et al., 2011).

After PBM is achieved, bones enter a maintenance phase where remodeling processes (ideally) keep bone mass relatively stable for some time. In healthy young adults, bone deposition and resorption remain tightly coupled, and BMD fluctuations are kept within a narrow range. Subtle perturbations, however, can result in remodeling imbalances as part of normal aging. Around the fourth decade of life, resorption gradually overtakes formation, resulting in a slow decline in total BMD (Hendrickx et al., 2015; Johnell & Kanis, 2005; Raisz, 2005a). This age-related bone loss accelerates in midlife, particularly in menopausal women due to estrogen withdrawal, as discussed below. The trajectory of bone health over the life course is shaped not only by biological timing but also by environmental exposures and life history, including nutrition, mechanical loading, and reproductive history. Consequently, public health efforts to

optimize PBM focus on early-life interventions such as adequate calcium and vitamin D intake, weight-bearing physical activity, and addressing endocrine or developmental disruptions during the growth years.

2.4 Bone Remodeling and Maintenance in Adulthood

Following the completion of skeletal growth, (i.e., the cessation of longitudinal bone expansion through epiphyseal plate fusion) bones continue to adapt and maintain themselves through bone remodeling. Remodeling enables the skeleton to adapt to evolving mechanical demands, repair microdamage, and maintain mineral homeostasis across the life course. This continuous turnover is essential for preserving structural integrity and adapt to physiological and biomechanical needs (White et al., 2011). Three main phases characterize the remodeling cycle. First, osteoclasts attach to the bone surface and dissolve the mineral matrix, resorbing old or micro-damaged bone. This resorption phase lasts a few weeks, during which osteoclasts dig small cavities (Howship's lacunae) into existing bone, releasing stored minerals like calcium and phosphate into the bloodstream. The subsequent reversal phase, which lasts a few days, halts resorptive activity as mononuclear macrophage-like cells clean up the eroded surface and lay down a protein-rich cement line in preparation for new bone deposition. Finally, osteoblasts are recruited to the site and produce osteoid (new organic matrix), which is then mineralized to refill the eroded cavity (Eriksen, 2010a; Zuo et al., 2012). As matrix deposition is completed, osteoblasts may become embedded in bone as osteocytes, become inactive osteoblasts or bone lining cells, or undergo apoptosis (programmed cell death). Through this tightly regulated sequence, bone remodeling balances degradation and renewal, ensuring the skeletal system

remains responsive and functionally competent throughout adulthood (Dallas and Bonewald, 2010).

The regulation of bone remodeling is complex and involves key systemic regulators such as parathyroid hormone (PTH) and active vitamin D (calcitriol), which increase bone resorption when blood calcium levels are low, and sex hormones estrogen and testosterone, which promote bone formation or reduce resorptive activity (Eriksen, 2010a). Essential to bone remodeling is estrogen, which triggers osteoclast apoptosis and supports osteoblast function; the postmenopausal reduction in estrogen levels is one of the major drivers of the sex-specific differences in BMD loss with age and risk of osteoporosis.

A crucial molecular signaling pathway is the RANK/RANKL/OPG system, which links osteoclast and osteoblast activity. Osteoblast-lineage cells produce RANKL, a ligand that stimulates osteoclast formation; they also produce osteoprotegerin (OPG), a decoy receptor that binds RANKL. The balance of RANKL and OPG production helps determine the level of bone resorption. This signaling process couples bone resorption and deposition, ensuring that, under healthy conditions, the skeleton is continually renewed without significant change in net BMD (Hadjidakis & Androulakis, 2006; Khosla, 2001; Raisz, 1999).

In adulthood, remodeling is the dominant mechanism of skeletal change (as opposed to modeling, which predominates during growth). In healthy adults, approximately 5–10% of total bone mass is estimated to turnover annually, renewing the skeleton entirely, on average, every 10 years (Raisz, 1999).

Notably, different parts of the skeleton are in different phases of the remodeling cycle, and the remodeling rate is not uniform throughout the skeleton. At any given time, a patchwork of bone removal and formation is silently occurring, allowing different regions to adapt to

variable stressors. The higher surface-area-to-volume ratio of trabecular bone undergoes remodeling far more rapidly than cortical bone. As a result, trabecular-rich regions (e.g., lumbar spine, trochanteric areas, and ends of long bones) are more metabolically active and often the first to show changes in BMD, particularly with age. Densely packed cortical bone remodeling takes longer, requiring osteoclasts to create small tunnels (Haversian systems) and refill them(Raisz, 1999).

Mechanical loading continues to influence bone remodeling even after skeletal ossification is complete. Habitual loading (or its absence) signals to osteocytes and bone lining cells that remodeling is needed; higher mechanical strains tend to promote deposition in the affected areas, and the absence of mechanical loading biases remodeling toward resorption and net BMD loss (Frost, 2003a; Kameda et al., 1997; Khosla et al., 2012; Ruff et al., 2006). This mechanosensitivity means that bones' adaptive capacity does not end in early adulthood when PBM is achieved.

Even a slight negative balance per remodeling cycle can lead to substantial bone loss, and with age, the coordination of remodeling may become less perfect, skewing toward net loss of bone tissue. This imbalance is particularly salient for females when the transition to menopause substantially reduces estrogen levels, removing a key restraint on osteoclast activity (Kameda et al., 1997). This leads to an upsurge of resorptive activity and the loss of several percentage points of their BMD in the first 5-10 years of postmenopausal life. Males, however, do not experience an equivalent sudden hormonal withdrawal; as a result, they tend to lose bone more gradually with age until the later decades of life when testosterone levels decline and as other age-related changes (e.g., reduced intestinal calcium absorption or compromised vitamin D synthesis) begin

to compromise bone maintenance (Finkelstein et al., 2008; Reeve et al., 1999; Wood et al., 1992).

2.5 Mechanotransduction and Skeletal Adaptation

Mechanotransduction is the process of converting mechanical forces into biological signals that guide bone remodeling. This process is critical to bone's ability to adapt, translating mechanical loads into cellular action (Riddle & Donahue, 2009). Osteocytes, trapped in bone matrix lacunae, serve as mechanosensors, detecting mechanical strain (i.e., deformation or change in shape) and fluid shear stress generated during physical activities. Similar to neurons, osteocytes feature extensive networks of dendritic processes that extend through tiny channels called canaliculi to enable intercellular communication and rapid transmission of mechanical signals (Burger & Klein-Nulend, 1999).

Mechanical loading of bones generates fluid movement within canaliculi surrounding mechanosensitive osteocytes. This fluid flow deforms osteocyte membranes and bends primary cilia, small cellular appendages crucial for sensing mechanical changes. These mechanical cues activate transmembrane receptors that link the extracellular matrix to the intracellular cytoskeleton, triggering intracellular signaling pathways and opening calcium ion channels. This, in turn, increases intracellular calcium levels, triggering osteocytes to rapidly produce two important signaling molecules: nitric oxide (NO) and prostaglandin E2 (PGE2) (Burger & Klein-Nulend, 1999; Eriksen, 2010a; Liedert et al., 2006; Riddle & Donahue, 2009).

NO is critical to mechanotransduction because it diffuses easily between cells to spread the mechanical signal. Additionally, NO is a vasodilator, increasing blood flow and, thus, nutrient transport to the remodeling region. PGE2 activates specific receptors on osteoblasts that trigger

bone formation activity. Simultaneously, mechanical stimulation modulates Wnt/β-catenin signaling, a crucial regulatory pathway in bone biology. Osteocytes respond to loading by suppressing sclerostin production, a molecule that normally inhibits Wnt signaling. Reduced sclerostin levels allow greater Wnt activity, significantly enhancing osteoblast proliferation, differentiation, and activity (Eriksen, 2010a; Galea et al., 2017; Oftadeh et al., 2015).

The Mechanostat Theory, proposed by Harold Frost, provides a quantitative framework for skeletal adaptation whereby bones maintain mechanical strains within optimal physiological ranges by altering their mass and geometry. When habitual mechanical strains fall below a minimal threshold, signaling pathways enhance bone resorption by osteoclasts, leading to reductions in bone mass and structural weakening. Conversely, strains exceeding typical physiological levels stimulate osteogenesis and strengthen bone to withstand increased mechanical demands. Dynamic loading is particularly osteogenic compared to static loading. Activities like running, jumping, and resistance training produce high-magnitude, dynamic mechanical strains that strongly stimulate osteoblast activity. Strain rate (how fast the bone is deformed) and frequency substantially influence bone adaptive responses, with higher rates and frequencies enhancing osteogenesis more effectively than lower-intensity loading (Frost, 2003a)

Mechanical loading's influence extends beyond PBM attainment or maintenance to also impact bone geometry and trabecular architecture alterations. Weight-bearing bones, like the femur and tibia, develop thicker cortical walls and more robust trabecular structures due to habitual mechanical stimuli (Bayraktar et al., 2004; Oftadeh et al., 2015; Wallace, Demes, et al., 2017). Conversely, bones subjected to minimal loading, such as those in sedentary individuals or astronauts experiencing microgravity, rapidly lose BMD and structural integrity, underscoring

mechanical loading's critical role in skeletal health (Foster, 2019; Fuchs et al., 2009; Greene & Naughton, 2006).

2.6 Biomechanical Regulation of Bone Mineral Density

Wolff's Law, formulated by 19th-century German anatomist Julius Wolff, posits that bone tissue aligns structurally along the lines of habitual mechanical stress (i.e., force applied to an area), enhancing mechanical strength (i.e., ability to resist applied forces) in areas subjected to regular mechanical loading. While Wolff's original 1892 formulation was overly rigid (a deterministic mathematical remodeling "law" later discredited), the core idea of bone's functional adaptation, that bone adapts to habitual mechanical loads, is foundational for biomechanists and biological anthropologists (Ruff 2006).

The Mechanostat Theory furthers this concept, proposing a biological feedback mechanism by which bone senses and responds to mechanical strain. Proposed by Harold Frost, the theory suggests that skeletal tissue continuously monitors mechanical loading through mechanosensing cells (e.g., osteocytes) and adjusts bone mass and architecture accordingly to maintain mechanical efficiency and structural safety. Strain, measured in micro strain (με), refers to the fractional deformation experienced by bone under load. In healthy bone, routine daily activities typically produce peak strains within a physiological range of approximately 1500–3000με. When mechanical loading falls below a "minimum effective strain" threshold (estimated around 800–1000με), the mechanostat signals that the bone is overbuilt (i.e., has more material than it needs to sustain the forces applied to it), prompting resorption. If habitual strains exceed the upper threshold of the safe range, however, the bone responds by adding mass or changing shape (net formation) to reinforce the structure and avoid the risk of fracture (Frost, 2003a).

This adaptive window of strain establishes what Frost termed a "strength safety factor," whereby bones in healthy, mechanically active individuals are maintained with a surplus of strength beyond habitual loads, protecting against spontaneous or non-traumatic fractures. The theory also accounts for clinically observed bone loss in conditions of disuse, such as bed rest, limb immobilization, or microgravity, where strain consistently falls below the resorptive threshold. Frost further developed the model to outline expected skeletal responses across the life span and across various clinical scenarios, offering function-based definitions for osteopenia and osteoporosis. By positioning bone as a dynamic, mechanosensitive organ, the Mechanostat Theory emphasizes the importance of habitual physical loading, particularly weight-bearing and high-impact activity, for the preservation of bone mass and structural integrity across the life course (Frost, 2003a; Oftadeh et al., 2015).

Perhaps most importantly for fossil enthusiasts and anthropological methods of activity reconstruction, bone's functional adaptation and the mechanostat theory emphasize that bone adapts *locally and specifically* to the strains it experiences and that skeletal heterogeneity in BMD and microarchitecture can often be used to infer past behavior (Ruff et al., 2006). For example, on average, the human femur and tibia (habitually loaded by standing and walking) often show greater cross-sectional area and cortical thickness to resist bending and compression, whereas the humerus remains more gracile (Chirchir et al., 2015).

Strain magnitude, the intensity of mechanical loading experienced by bone tissue, directly influences bone mass accrual. Strain magnitudes from by high-impact activities like running or jumping, stimulate bone deposition and increase density. Conversely, prolonged periods of low strain magnitudes, characteristic of sedentary lifestyles or immobilization, enhance resorption, diminishing bone strength (Rubin & Lanyon, 1985). Strain rate, or the speed

at which mechanical loads are applied, also influences bone adaptation. Rapidly applied mechanical strains elicit more significant osteogenic responses than slowly applied forces (Ehrlich & Lanyon, 2002). High-frequency loading activities (plyometric exercises), such as box jumps or burpees, increase BMD more effectively by inducing rapid and repetitive mechanical stimulation(Fuchs et al., 2009).

Directional loading influences bone structural optimization, aligning trabecular patterns and cortical thickness to improve resistance to prevalent mechanical forces. Bones do not randomly adapt their structure to habitual loading but directionally to enhance resistance to specific strain encountered during routine physical activities (Amling et al., 1996). This adaptive mechanism optimizes bone strength-to-weight ratios, efficiently distributing bone mass only where needed (Frost, 2003a; Ruff et al., 2006).

2.6 Adaptation Across the Life Course

The interaction between mechanical loading and bone remodeling changes considerably throughout an individual's life. During periods of growth and development, (e.g., childhood and adolescence) when modeling is active, mechanical forces strongly influence bone morphology, and physical activity during the growth years can lead to lasting increases in bone cross-sectional dimensions and density (Greene & Naughton, 2006; Gunter et al., 2012). Studies of young athletes demonstrate greater bone mass accrual or thicker cortical bone in the loaded limbs than non-athletes, reflecting bone’s responsiveness when modeling capacity is high (Gustavsson et al., 2003).

On average, by the end of the second decade of life, individuals achieve PBM, a product of genetics, nutrition, and hormones, but also activity: higher mechanical loading during growth

generally elevates the peak, effectively “banking” BMD that may buffer the skeleton against the adverse effects of age-related bone loss later in life. Once skeletal maturity is reached, the ability to dramatically alter bone shape diminishes, but remodeling continues to allow adaptation in bone’s internal structure and mineral uptake and, therefore, change bone strength. Numerous studies indicate that the magnitude of adult bone’s adaptive response is blunted compared to that of juveniles; however, adult bone structure still reflects adult loading to a meaningful degree (Cooper et al., 1995; Eriksen, 2010a; Foster, 2019; Raisz, 1999; Rizzoli et al., 2009).

Mechanostat setpoints may shift across the life course, such that the mechanical strain required to stimulate new bone formation rises with age, while the skeletal safety margin narrows. This age-related alteration is partly attributable to cellular senescence: osteoprogenitor cells in older adults exhibit reduced proliferative and differentiation potential, and osteoblasts and osteocytes become less responsive to mechanical stimuli (Frost, 1997, 2003a; Ruff et al., 2006) Even when habitual loading remains similar, the mechanostat’s feedback loop weakens, that is, senescent osteocytes may fail to transduce mechanical signals effectively, contributing to an imbalance where resorption incrementally outpaces formation. Compounding this is a suite of age-associated factors (e.g., diminished calcium or vitamin D absorption, declining anabolic hormone levels, and chronic low-grade inflammation) that impair bone’s ability to adaptively respond to strain (Ehrlich & Lanyon, 2002; Liedert et al., 2006; Riddle & Donahue, 2009; Wallace, Demes, et al., 2017).

These biological changes underpin the typical BMD trajectory across the life span. Following rapid skeletal accrual in childhood and adolescence, BMD peaks in early adulthood and then begins to decline in the fourth decade of life. This gradual loss reflects a cumulative remodeling imbalance, as the ability to fully restore microdamage diminishes with each

remodeling cycle (Hendrickx et al., 2015; Raisz, 2005a). In women, this process accelerates dramatically during menopause, when estrogen withdrawal leads to a transient but sharp increase in bone turnover. Without sufficient hormonal replacement or mechanical stimulus, resorption may exceed formation by as much as 2–3% per year over several years (Ettinger et al., 1985; Nguyen et al., 1995). Estrogen's regulatory role is crucial. It promotes osteoblast survival and suppresses osteoclast activity; its loss, therefore, triggers unchecked osteoclast activity and resorption (Kameda et al., 1997; Khosla et al., 2012; Popat et al., 2009). Concurrently, many women reduce their physical activity levels during midlife, further exacerbating bone loss (Kistler-Fischbacher et al., 2021; Martyn-St James & Carroll, 2008).

Men also lose BMD with age, but more gradually; they lack an abrupt hormonal transition analogous to menopause and demonstrate higher BMD on average (Gildee & Kramer, 2025; Ruff et al., 2006). Regardless of sex, by the eighth decade of life, humans exhibit reduced BMD and increased cortical porosity, consequences of a lifetime of subtle imbalances in remodeling (Chandra & Rajawat, 2021; Johnell & Kanis, 2005; Raisz, 2005a).

2.7 Human Reproduction, Energetics, and Skeletal Trade-offs

Successful reproduction exerts substantial metabolic and mechanical demands on the female skeleton (Agarwal et al., 2005; Gur et al., 2003; Hwang et al., 2016; Jasienska, 2020c; Jasienska et al., 2017). From an evolutionary and life history perspective, these demands reflect critical trade-offs between reproductive success and long-term somatic maintenance. Life History Theory, which emphasizes how organisms allocate limited energetic resources among competing demands of growth, maintenance, and reproduction, offers a valuable lens to interpret female BMD variation across the life course (Madimenos, 2015a; Nettle & Frankenhuis, 2019; Stearns,

1989). Central to this framework is the Cost of Reproduction Hypothesis, which posits that the energetic investments required for reproduction come at a cost to other physiological processes, including skeletal growth and integrity (Jasienska, 2009, 2020a; Nilsson & Svenssonn, 1996; Ziomkiewicz et al., 2016).

Pregnancy and lactation are characterized by substantial skeletal calcium mobilization to support fetal skeletal growth and milk production (Madimenos, 2015a; Madimenos et al., 2012; Prentice & Prentice, 1988). During pregnancy, maternal calcium absorption increases, mediated by elevated estrogen levels, generally leading to modest gains or stable maternal bone mass. Lactation, however, temporarily reduces estrogen to postmenopausal levels and dramatically increases calcium demand, resulting in considerable bone resorption, particularly noticeable in trabecular-rich regions such as the lumbar spine and hip (Jasienska, 2020a; Madimenos, 2015a; Prentice & Prentice, 1988). Although postpartum recovery is typical after weaning, the extent of bone regeneration depends heavily on maternal nutrition, duration of lactation, parity, and interbirth intervals; closely spaced pregnancies reduce opportunities for skeletal recovery, potentially leading to cumulative BMD loss (Jasienska, 2009, 2020a; Madimenos, 2015a; Madimenos et al., 2012, 2020; Song et al., 2017; Stieglitz et al., 2015a; Ziomkiewicz et al., 2016)

These physiological challenges reflect an evolutionary tension between immediate reproductive imperatives and long-term skeletal health. The Disposable Soma Theory suggests that organisms prioritize reproduction over somatic maintenance in resource-constrained environments, accelerating senescence (Kirkwood & Rose, 1991a) Applied to human females, this theory implies that high reproductive effort over the life course (e.g., multiple pregnancies

and prolonged lactation) may redirect resources away from bone modeling or remodeling, raising the risk of osteoporosis later in life (Jasienska, 2020a)

Support for these trade-offs is substantial. A 2016 study in a high fertility population in Southern Poland found that postmenopausal women with high parity exhibited elevated biomarkers used to assess whole-body oxidative stress in humans (specifically, 8-OHdG, Cu-Zn SOD, and TBARS), indicating increased cellular aging among these women (Ziomkiewicz et al., 2016). Similarly, research among Tsimane women, a high-fertility subsistence population, demonstrated that greater lifetime reproductive effort was associated with lower BMD, especially when accompanied by short birth spacing and early reproductive onset (Stieglitz et al., 2015a). Some populations, however, may experience buffering against the long-term effects of reproduction. Among Shuar women, also part of a forager-horticulturalist group, no significant negative associations were found between parity or lactation duration and postmenopausal BMD, potentially due to their reduced pathogen burden or increased body mass indices. In fact, earlier menarche correlated with higher BMD, suggesting that developmental timing and early-life nutritional status may better predict postmenopausal BMD outcomes(Madimenos et al., 2012, 2020).

These context-specific findings highlight the role of developmental and ecological conditions. Several theoretical frameworks have been proposed arguing that early-life environments shape adult physiological trajectories, potentially affecting both reproductive and skeletal outcomes. In resource-limited settings, these trajectories may amplify reproductive costs, while in better-nourished populations, they may support recovery and resilience (Eisenberg & Kuzawa, 2018; Gluckman & Hanson, 2004; Kuzawa, 2005, 2007; McDade et al., 2016).

2.8 Other Life History and Evolutionary Perspectives on Bone Density

Evolutionary medicine offers several, not mutually exclusive, explanations for why the human skeleton may have evolved to deteriorate with age. Antagonistic pleiotropy, when applied to aging, suggests that osteoporosis may be an unintended byproduct of adaptations that had benefits earlier in life (Jasienska et al., 2017; Kirkwood, 2002; Kirkwood & Rose, 1991a; López-Otín et al., 2023; Madimenos, 2015a). Natural selection strongly shapes traits that improve early-life survival and reproductive success but has a much weaker influence on traits expressed in post-reproductive years. Genetic or developmental factors that benefit skeletal growth and fertility in early adulthood might carry a trade-off that compromises bone remodeling in later adulthood. In this way, deleterious effects that manifest in old age may persist in a population if coupled with improved fitness.

Similarly, the disposable soma hypothesis posits that organisms have a finite energy budget to be allocated to reproduction or somatic maintenance. Evolution requires reproduction (the passing on of genetic material); somatic maintenance (including bone remodeling) may be comparatively underfunded. (Gurven et al., 2016; Kirkwood, 2002; Madimenos, 2015a). In bone remodeling, there may be a tendency to invest heavily in building bone mass through the reproductive period (to support locomotion, resource acquisition, and childbearing) and to invest less in repairing bone in later life when reproductive capacity has ended (Gildee & Kramer, 2025; Madimenos, 2015a). This could partially explain why age-related bone loss is most pronounced in the postmenopausal period.

During pregnancy, women experience elevated estrogen levels, increased calcium absorption, and increased body mass, often resulting in a slight increase in maternal bone mass. Without sufficient nutritional resources, bone can be transiently resorbed to provide calcium to

the fetus, though estrogen helps minimize net bone loss in pregnancy. Postpartum females typically lose BMD (as calcium is mobilized for milk production and estrogen levels drop to postmenopausal levels temporarily); however, bone loss tends to be temporary and largely recovers after weaning. Some evolutionary biologists (Gurven et al., 2016; Jasienska, 2009, 2020a; Kramer, 1998; Madimenos, 2015a) argue that the relatively higher osteoporosis risk in women is, in part, a trade-off for the energetic demands of gestation and lactation, an evolutionary compromise where favoring reproduction over long-term skeletal maintenance, which natural selection did not strongly influence as fitness-threatening osteoporotic fractures would not occur until well after the reproductive years.

Another evolutionary explanation could be related to our species' exceptional longevity. Evolutionary medicine's mismatch theory suggests the modern rise in rates of osteoporosis (and other chronic diseases more broadly) to novel changes in human lifestyles and environment compared to the environment of evolutionary adaptedness (Gagnon et al., 2009; Gluckman et al., 2019; Madimenos, 2015a). Only in the last one hundred years or so have humans regularly lived into their 70s or 80s, when osteoporosis and related fractures are most common. The increase in human lifespan (initially through evolutionary changes and more recently through cultural and medical advances) permits sufficient time for the degenerative aspects of aging to manifest in bone, framing osteoporosis as a disease of modernity. In fact, the prevalence of osteoporotic fractures in prehistoric or early historic populations appears to have been much lower than in contemporary societies (S. C. Agarwal & Grynpas, 1996).

Two key mismatches are often blamed for the novelty of global osteoporosis rates. First is the reduced physical activity experienced by modern industrialization, resulting in inadequate mechanical loading of the skeleton to sufficiently stimulate bone maintenance. Humans living in

less industrialized regions, forager-horticulturalists, and subsistence farmers typically have far greater daily loading activity (e.g., walking long distances, carrying supplies and offspring), which helps preserve bone mass (Fuchs et al., 2009; T. M. Ryan & Shaw, 2015). In contrast, humans living in more industrialized contexts, and particularly those in predominantly white, educated, industrialized, rich, and democratic (WEIRD) nations, spend large portions of time sitting, driving, or doing low-impact activities, depriving bone of the habitual mechanical strain it requires to maintain BMD (Healy et al., 2011).

Second, modern medicine and improved access to nutrition allow a comparatively greater percentage of the population to survive to advanced age, potentially exposing genetic predispositions toward bone loss previously obscured by high mortality rates (Gurven & Kaplan, 2007; Raisz, 1999). Further, on average, mothers in industrialized regions tend to have fewer pregnancies and shorter breastfeeding duration than those in more traditional societies (InterLACE Study Team, 2019; Madimenos et al., 2012); this alters lifetime hormone exposure patterns and might influence bone density trajectories (although the net effect of fewer reproductive cycles on long-term bone health remains poorly understood) (Nguyen et al., 1995). Evolutionary mismatch theory suggests that the human capacity for bone maintenance evolved in an environment where constant activity and a certain life expectancy were the norm; deviating from that template yields some negative consequences for bone health (Gluckman et al., 2019).

Locomotor adaptations and accompanying morphological changes should not be ignored when considering the origins of age-related bone loss. The evolution of habitual bipedalism in hominins fundamentally altered skeletal loading patterns, redistributing ground reaction forces and promoting structural specialization in the limbs (Chirchir, 2019; Richmond et al., 2001; T. M. Ryan & Shaw, 2015; Sylvester, 2006). Necessary anatomical changes improved bipedal

locomotor efficiency, particularly for endurance walking and running (Kramer, 1999; Steudel, 1996; Steudel-Numbers & Tilkens, 2004; Taylor & Rowntree, 1973); however, they also coincided with an evolutionary trend toward a more gracile skeleton. Modern humans exhibit unique and significantly lower trabecular-to-cortical bone ratios throughout the appendicular skeleton relative to great apes and other hominins (Chirchir, 2019). This reduction is particularly striking in weight-bearing regions such as the femoral head and distal tibia, where increased loading from habitual bipedalism would have presumably demanded increased capacity for absorbing and redistributing ground reaction forces (T. M. Ryan & Shaw, 2015). Reduced BMD in weight-bearing regions despite increased mechanical demands suggests the possibility of an evolutionary trade-off such that reduced bone mass may have enhanced metabolic efficiency at the cost of structural resilience with age.

Further, the gracilization of anatomically modern human skeletons appears to be a late-Holocene phenomenon, emerging alongside increased sedentism and cultural buffering rather than during the early evolution of *Homo* (Chirchir, 2019; Chirchir et al., 2015; T. M. Ryan & Shaw, 2015). Additionally, bone's responsiveness to mechanical stimuli declines with age, so a structurally lighter skeleton, while efficient during reproductive years, may become vulnerable in late life when remodeling lags behind mechanical need. The history of hominin locomotor adaptations and accompanying morphological changes suggest that bone fragility in aging modern humans is not simply a byproduct of aging but the downstream cost of a broader evolutionary strategy emphasizing energy conservation, locomotor economy, and socio-environmental complexity.

It is important to note that evolutionary explanations do not imply determinism; they provide context in which to situate our current understanding of human biology. Modern

populations exhibit genetic variation (Estrada et al., 2012), nutritional access (Shams-White et al., 2017), and patterns of physical activity (Gunter et al., 2012) which contribute to differences in BMD. Comparative studies document distinct peak bone mass levels (Berger et al., 2010; Bonjour et al., 2009; Weaver et al., 2016) and rates of age-related bone loss (Chan & Duque, 2002) among groups, reflecting the combined influence of heredity and environment. High levels of mechanical strain can lead to bones that approach the upper limits of density and robustness for our species, potentially protecting against osteoporotic fractures; however, nutritional deficiencies or chronic disease can result in osteoporosis even in midlife, highlighting how environment and individual history modulate any baseline evolutionary design.

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Chapter 3: NHANES 1999-2018: Structure, Methods, and Utility for Skeletal Health Research

3.1 NHANES Program Overview

The National Health and Nutrition Examination Survey (NHANES), administered by the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS), has provided a critical infrastructure for health surveillance and population-based research since transitioning to a continuous program in 1999. NHANES is uniquely positioned to evaluate national health trends because it combines comprehensive self-reported health and lifestyle data with detailed physical examinations and laboratory testing. NCHS utilizes NHANES to monitor the health and nutritional status of the civilian, non-institutionalized U.S. population, offering nationally representative estimates that inform public health policy and clinical guidelines. Data collection occurs in two-year cycles, with approximately 10,000 participants surveyed per cycle. These individuals are selected using a complex, multistage sampling strategy designed to reflect the diversity of the U.S. population and to oversample groups at greater risk of health disparities, such as older adults, children, racial/ethnic minorities, and low-income individuals.

3.1.1 Data Collection and Ethical Oversight

NHANES protocols are reviewed and approved by the NCHS Ethics Review Board. Participants provide informed consent before participation, and special protections are in place for minors and other vulnerable populations. Interview and exam protocols are standardized across Mobile Examination Center (MEC) locations and time periods. This methodological consistency is crucial for the use of NHANES in temporally relevant and cross-sectional

analyses. Using clinical-standard equipment, detailed examiner training, and continuous quality oversight minimizes systematic errors and ensures the reproducibility of key health measures, such as BMD and LTL.

3.1.2 Confidentiality

The NHANES Data used in this dissertation is publicly available. All information relating to or describing identifiable characteristics of individuals, a practice, or an establishment will be used only for statistical purposes. NCHS staff, contractors, and agents will not disclose or release responses in identifiable form without the consent of the individual or establishment in accordance with section 308(d) of the Public Health Service Act (42 U.S.C. 242m(d)) and the Confidential Information Protection and Statistical Efficiency Act or CIPSEA (44 U.S.C. 3561-3583). In accordance with CIPSEA, every NCHS employee, contractor, and agent has taken an oath and is subject to a jail term of up to five years, a fine of up to $250,000, or both if they willfully disclose any identifiable information about a participant. In addition to the above-cited laws, NCHS complies with the Federal Cybersecurity Enhancement Act of 2015 (6 U.S.C. §§ 151 and 151 note), which protects federal information systems from cybersecurity risks by screening their networks.

3.1.3 On Sex and Gender

This dissertation uses sex-specific (e.g., male, female) and gender-specific (e.g., men, women) terminology as used in the primary literature and accordance with the NHANES dataset. The National Health and Nutrition Examination Survey collects “gender” data using a binary self-report form with the options “male” and “female,” which are treated here as proxies for

biological sex. Accordingly, binary gendered terms are used here when referencing NHANES participants, with gender assumed based on questionnaire structure and responses.

It is recognized that both sex and gender exist beyond binary classifications. “Sex” is not a singular trait but an assemblage of characteristics, including chromosomes, gonads, hormone profiles, reproductive anatomy, and secondary sexual features, that may not align predictably within individuals (McLaughlin et al., 2023). Similarly, both sex and gender exist along spectra, and strict binary labels obscure the natural variation in sexual development, morphology, and behavior found across human populations (Fuentes, 2025). Collapsing this complexity into a single term oversimplifies biological variation and much of the complexity inherent in sexual phenotypes.

NHANES restricts sex/gender classification to two mutually exclusive options, limiting how participants can be categorized in large-scale epidemiological studies. While this dissertation works within those constraints, it recognizes that such limitations are methodological, not biological, and that efforts to improve the inclusivity and accuracy of population-level health data must move beyond binary frameworks.

NHANES does not explicitly exclude intersex or transgender participants through its recruitment criteria; however, its sampling, data collection, and public data structures are not well-equipped to identify or analyze these populations. Further, NHANES uses binary categories ("male" and "female") based on self-report and observation, and in some cases, assigns a category based on respondent appearance when unclear. No survey items explicitly ask about sex assigned at birth or transgender status. As such, transgender and intersex individuals may be included, but their identities are not captured or coded in publicly available datasets, preventing identification or subgroup analysis.

This represents a limitation in data collection and analytic representation, not an intentional exclusion. An estimated 0.39–0.6% of U.S. adults identify as transgender (approximately 1.1–1.7 million people) (Meerwijk & Sevelius, 2017), while 0.018–1.7% may be intersex depending on definitional criteria (Fausto-Sterling & Sax, 2002). NHANES does not systematically identify or categorize these individuals due to the absence of adequate questions about gender identity or intersex status; however, their inclusion or omission in my samples is unlikely to be a source of error or misrepresentation of the general population.

3.2 Sampling Design and Demographics

3.2.1 Sampling Design Overview

The National Health and Nutrition Examination Survey (NHANES) uses a complex, multistage, stratified probability sample design from 1999 to 2018 to produce nationally representative estimates of the non-institutionalized civilian U.S. population. Data were released in 2-year cycles to balance timeliness, confidentiality, and statistical reliability while maintaining a consistent methodology across most periods to facilitate comparability and analytic flexibility.

Since its 1999 re-launch as a continuous survey, NHANES has used a four-stage sample design: (1) selection of primary sampling units (PSUs) (typically counties or groups of counties), (2) segments within PSUs (census blocks), (3) households within segments, and (4) individuals within households. PSUs were selected with probabilities proportional to a measure of size (PPS) based on demographic targets, such as age, sex, race/Hispanic origin, and income (Chen et al., 2020; Curtin et al., 2012).

The sampling strategy emphasized oversampling to improve reliability for subpopulations of public health interest. From 1999–2006, oversampled groups included

Mexican Americans, non-Hispanic Black individuals, adolescents, older adults (60+), and, beginning in 2000, low-income individuals and pregnant women (Curtin LR et al., 2012). For 2007–2014, this was modified to include all Hispanic persons, not just Mexican Americans, as well as low-income non-Hispanic whites and other individuals(Curtin LR et al., 2013; Johnson CL et al., 2014). Between 2011 and 2018, the oversampling frame expanded to include non-Hispanic Asian individuals, with income thresholds raised from 130% to 185% of the federal poverty level beginning in 2015 to align with WIC eligibility criteria (Chen TC et al., 2020; Johnson CL et al., 2014).

3.2.2 Domain and Precision Considerations

NHANES aimed to provide estimates for domains defined by race/ethnicity, income, sex, and age. Domain-specific sampling rates were calculated to ensure statistical precision, targeting approximately 150–420 examined persons per domain to satisfy conditions for standard errors and detectable differences between groups (Curtin LR et al., 2012; Johnson CL et al., 2014). Analysts were advised to combine multiple 2-year cycles, especially for rare conditions or smaller demographic groups, to achieve adequate power (Chen TC et al., 2020).

3.2.3 Operational Implementation

Field operations were conducted using mobile examination centers (MECs) (Figure 1), traveling to 15 study locations annually. Each MEC was staffed and equipped to perform standardized health exams, including physical measurements, laboratory testing, and interviews(Curtin LR et al., 2013; Johnson CL et al., 2014). Within each PSU, approximately

300–600 persons were sampled to yield a target of 5,000 examined participants per year (Chen TC et al., 2020; Johnson CL et al., 2014).

3.2.4 Weighting and Estimation

Sample weights were computed to adjust for differential selection probabilities, nonresponse, and post-stratification calibration to U.S. population totals. For the 2015–2018 cycles, weights were also adjusted for education and area-level household income to address known sources of nonresponse bias (Chen TC et al., 2020). Variance estimation used masked variance units based on strata and PSU design variables, facilitating appropriate standard error calculations in public use (Chen TC et al., 2020; Curtin LR et al., 2012, 2013; Johnson CL et al., 2014).

3.3 Data Collection and Mobile Examination Centers

NHANES employs a standardized two-part data collection process. In the first phase, trained interviewers conduct in-home interviews to gather information on participant demographics, dietary habits, medical history, lifestyle behaviors, and reproductive history. The second phase consists of a comprehensive physical examination conducted in a Mobile Examination Center (MEC), a traveling clinical site outfitted with diagnostic and laboratory equipment. MECs allow for standardization of procedures regardless of geographic location, ensuring uniformity in collecting objective health data such as blood pressure, anthropometry, body composition, and blood/urine biomarkers. Licensed medical professionals and trained technicians administer examinations under strict protocols (Chen TC et al., 2020).

3.4 DXA Examination and Bone Density Measurement

A critical component of NHANES's skeletal health surveillance is its use of dual-energy X-ray absorptiometry (DXA), the clinical gold standard for assessing BMD and body composition. Since 1999, NHANES has implemented whole-body DXA scans for adults aged 20 to 59 years, initially using Hologic QDR 4500A (see Appendix A) fan-beam densitometers and later transitioning to Hologic Discovery A systems (see Appendix A) beginning with the 2011–2012 cohorts. Both systems emit X-rays at two distinct energy levels, which are differentially attenuated by bone and soft tissue. These attenuation profiles are used to distinguish bone mineral content (BMC) from lean and fat mass, enabling the calculation of areal bone mineral density (BMD, measured in g/cm²), as well as fat mass, lean mass, and regional body composition (Center for Health Statistics, 2016, 2018).

The underlying physics of DXA technology is based on the differential absorption of X-rays by tissues of varying densities. DXA uses a narrow or fan-shaped beam of X-rays generated at two different photon energy levels. These beams pass through the body and are differentially attenuated depending on the type of tissue encountered. A detector on the opposite side of the scanner captures the transmitted X-rays, and a proprietary algorithm calculates BMC by analyzing the difference in attenuation between the two energy levels. Soft tissue composition is then derived by subtracting the bone signal from the total signal in each region of interest. Areal BMD is computed by dividing BMC by the projected area of the bone in the two-dimensional scan field in g/cm². This method provides high precision and low radiation exposure; however, it is a two-dimensional measurement and cannot provide information on volumetric geometry or bone microarchitecture (Genant et al., 1996).

Scans were conducted in NHANES Mobile Examination Centers (MECs) by certified radiologic technologists following standardized protocols. Safety was a priority: all women of childbearing age underwent pregnancy screening and were excluded if pregnant, while individuals exceeding device size constraints were also excluded to maintain scan integrity. The QDR 4500A supported a maximum participant weight of approximately 300 pounds (136 kilograms), while the Discovery A increased the allowable limit to 450 pounds (204 kilograms). Both systems limit the maximum scan field to a width of approximately 60 cm (24 in). Participants exceeding this width, or whose anatomy could not be fully captured in the field of view, were excluded, or their scans were marked incomplete. Additionally, individuals had to lie flat and remain still for the duration of the scan, excluding some individuals with mobility impairments, pain, or medical devices (Center for Health Statistics, 2016, 2018).

The DXA module provides comprehensive data on total body BMD and region-specific values for clinically significant sites, including the femoral neck, lumbar spine, trunk, arms, legs, pelvis, and thoracic spine. These regional measures are particularly relevant in studies assessing fracture risk or evaluating bone loading patterns in life-history analyses. Over the 1999–2018 period, NHANES produced one of the most extensive databases of BMD measures available globally, forming the empirical foundation for clinical guidelines, public health benchmarks, and anthropological models of skeletal variation.

3.4.1 DXA Data Acquisition and Quality Control

To ensure consistency and accuracy in DXA-derived measurements across survey cycles and study locations, NHANES implemented rigorous quality control protocols. Every morning prior to participant scanning, technologists performed calibration procedures to verify scanner

performance and stability. Additional weekly quality assurance tests were conducted to monitor scanner accuracy, edge detection, and radiographic uniformity. Radiologic technologists were required to undergo annual recertification and retraining to standardize performance across field teams and survey cohorts.

Radiation exposure was minimal and well within acceptable public health thresholds. The effective dose from a whole-body DXA scan was estimated at 4.2 to 5.2 μSv, equivalent to less than two days of natural background radiation or a fraction of a conventional chest X-ray. To minimize inter-technician variability, NHANES centralized scan processing and quality review. The University of California, San Francisco, served as the NHANES DXA Quality Control Center throughout most of the study period, systematically reviewing scan images for motion artifacts, improper participant positioning, incomplete anatomical coverage, and adherence to imaging protocol. Scans that did not meet quality thresholds were excluded from analysis, and regular feedback was provided to field teams to ensure protocol compliance (Kelly et al., 2009).

3.4.2 Utility for Skeletal Health Research

NHANES's DXA data provide one of the most comprehensive, population-based resources for assessing skeletal health in the United States. The survey's nationally representative sampling design, combined with its rigorous imaging methodology and breadth of demographic and health data, allows researchers to model age-related trends in bone density, estimate the prevalence of osteopenia and osteoporosis, and evaluate disparities in skeletal health across sex, race/ethnicity, income level, and behavioral exposures. Multiple studies using NHANES data have documented that non-Hispanic Black adults exhibit higher mean BMD and lower fracture

risk compared to non-Hispanic White adults, potentially due to differences in muscle mass, bone geometry, and loading history during growth and adulthood.

Site-specific BMD data from the proximal femur and lumbar spine have been used to evaluate the clinical burden of osteoporosis using World Health Organization T-score thresholds, while whole-body DXA measures have supported analyses of lean mass, fat distribution, and bone loading (Dimai, 2017). The addition of IVA scans in 2013 further enhanced the ability to identify vertebral fractures and aortic calcifications, two major predictors of morbidity that were previously difficult to assess in large epidemiological surveys. Further, the repeated cross-sectional design of NHANES allows researchers to track secular trends in BMD and body composition across decades, supporting investigations into the effects of medication use (e.g., bisphosphonates), changes in physical activity, nutritional intake, or population aging on skeletal outcomes.

Beyond clinical applications, NHANES DXA data have supported a growing body of anthropological and epidemiological research exploring the intersection of biomechanics, life history, and health disparities (Dimai, 2017; Kelly et al., 2009). As such, the NHANES DXA archive not only serves as a foundation for public health surveillance and guideline development, but also as a unique resource for modeling the biocultural determinants of adult skeletal variation in contemporary populations.

3.5 Leukocyte Telomere Length and Aging Biomarkers

NHANES also enables the integration of skeletal data with broader biomarkers of systemic aging. During the 1999–2002 cycles, NHANES measured leukocyte telomere length (LTL) in a subsample of participants using quantitative polymerase chain reaction (qPCR).

Telomeres are DNA-protein structures that cap the ends of chromosomes and shorten with each cell division. Accelerated telomere attrition is associated with cellular aging and an increased burden of chronic diseases. Studies have linked shorter LTL to reduced BMD, suggesting a shared pathway between skeletal and systemic aging.

This biomarker complements BMD in life history research by capturing long-term physiological costs of reproduction and somatic maintenance. NHANES allows for the examination of how reproductive variables (e.g., parity, age at menarche, age at first birth) relate to both skeletal and cellular aging markers. While LTL data are limited to the 1999–2002 cycles, their inclusion remains valuable for assessing trade-offs consistent with life history theory, such as the cost of reproduction hypothesis.

3.6 Limitations for Life History and Aging Research

Despite its comprehensive scope, NHANES is subject to limitations that must be considered when applying it to life history and aging research. Foremost, its cross-sectional design precludes direct observation of change over time within individuals. Life history processes, particularly those related to trade-offs between reproduction and somatic investment, are ideally assessed using longitudinal data. NHANES provides population-level snapshots rather than individual trajectories, necessitating careful interpretation of inferred patterns.

Further, some variables critical to life history theory—such as energy expenditure, breastfeeding intensity, physical labor, and early developmental nutrition—are imperfectly captured or not included. Measures such as physical activity are self-reported and may be subject to recall bias. While parity and age at first birth are recorded, interbirth intervals can only be

calculated as an average, and lactation data does not include duration. These limitations complicate efforts to quantify cumulative reproductive costs.

Additionally, LTL measures were only collected from 1999 to 2002, which restricted the sample size and prevents the analysis of longitudinal trends in cellular aging. Researchers interested in integrating BMD and LTL must limit their focus to this subset and contend with sample representativeness or risk statistical power issues.

NHANES remains an indispensable tool for life history research, offering unparalleled access to high-quality, representative data on skeletal health and aging. Its integration of DXA, LTL, and extensive reproductive, nutritional, and demographic variables makes it uniquely suited to test life history hypotheses at scale, despite its limitations and organizational quirks.

3.7 Summary of NHANES Data

NHANES 1999–2018 provides a publicly available, comprehensive, and standardized platform for analyzing the intersections of skeletal biology, reproductive life history, and systemic aging. This enables researchers to investigate the complex trade-off that may shape human health across the life course by combining clinical measures such as DXA-based BMD with aging biomarkers like leukocyte telomere length and a breadth of health-related covariates. As skeletal fragility and other aging-related health conditions gain global health relevance, NHANES provides a wealth of data to inform anthropological theory and clinical practice.

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Chapter 4: ASSOCIATION BETWEEN PARITY AND BONE MINERAL DENSITY

Preface

This manuscript has been published as an original article in the American Journal of Human Biology under the title “Association Between Parity and Bone Mineral Density in the National Health and Nutrition Examination Survey” and authored by Cristina Gildee and Patricia Ann Kramer.

4.1 ABSTRACT

Objective: Bone remodeling relies on a dynamic process of concurrent deposition and resorption of bone material, which regulates bone mineral density (BMD), a critical component of overall bone health. Chronic dysregulation of the remodeling process during an individual's life can result in low BMD, osteoporosis, reduced mineral reserves and/or increased fracture risk. Prior studies have investigated the link between parity and BMD, positing that one cost of. reproduction is increased bone resorption above deposition, resulting in net BMD loss. Further, bone remodeling is sensitive to repetitive mechanical loading, suggesting that differences in bone loading could modify associations between parity and BMD. We seek to understand how reproductive investment (using parity as a proxy) challenges bone remodeling.

Methods: We examined associations between parity and regional BMD using anthropometric, dual-energy x-ray absorptiometry, and questionnaire data from the National Health and Nutrition Examination Survey (2007–2018 cohorts; n = 5144).

Results: In unadjusted linear regressions, higher parity was associated with lower BMD in all regions except the thoracic spine, arms, and total BMD ($p < 0.004$). In regressions adjusting for BMI and age, parity was positively associated with BMD in the pelvis, arms, and total BMD ($p < 0.004$). The maximally controlled models, which adjust for race/ethnicity, sedentary time, poverty income ratio, and lifetime estrogen exposure, among other health and lifestyle variables, yielded similar results.

Discussion: Our results suggest that more rigorous statistical modeling and selection of reproductive cost variables may help explicate the biological mechanisms underlying conflicting parity-BMD associations and their impact on bone health and aging.

4.2 INTRODUCTION

Bone mineral density (BMD), the mass of calcium and other minerals measured in grams per unit of bone area, is a crucial indicator of bone health. Pathological or chronic imbalances between bone deposition and resorptive remodeling processes can result in measurable net BMD loss, compromising the bone's structural integrity and increasing an individual's overall morbidity and mortality risk (Melton 1997; Reginster and Burlet 2006). Several sex-specific factors related to reproduction are believed to be associated with BMD over the life cycle and are posited to be major contributors to the sex bias in the prevalence of BMD-- related disease (Madimenos et al. 2012). For example, gestation, parturition, and successful childrearing require substantial energetic resources (Dufour and Sauther 2002). Life history theory—which posits that greater energetic investment in reproduction could constrain available resources for somatic maintenance—can be applied to investigate possible reproductive trade-offs in the ability of bone

tissue to maintain itself and respond to mechanical loading and physical activity (Kirkwood and Rose 1991; Madimenos 2015). Parity, or the total number of live births, has been associated with BMD in several populations; however, the direction and strength of that association are inconsistent among studies (Gur et al. 2003; Hillier et al. 2003; Lee 2019; Madimenos et al. 2012; Murphy et al. 1994; Song et al. 2017; Specker and Binkley 2005; Stieglitz et al. 2015; Yang et al. 2022). Pregnancy and breastfeeding are each expected to result in BMD loss as minerals are mobilized from bone to support fetal growth as energetic demands on the mother increase (Prentice 2003; Prentice and Prentice 1988; Vargas Zapata et al. 2004). It remains unclear, however, if this effect is balanced by compensatory systems in the mother and, importantly, if and how these costs compound over multiple children, with decreased birth spacing, hormone use, or the duration of breastfeeding. These variations in reproductive history over the lifespan may result in contradictory results surrounding these associations and proposed causal mechanisms.

Further, skeletal regions are subjected to differential exposure to ground reaction and muscle forces as individuals move about their environment. The direction and intensity of these forces dictate the development, morphology, microarchitecture, and density of the bony tissue. As a result, BMD necessarily varies within and between anatomical regions, allowing bone to resist excessive deformation or structural failure in response to the physical demands of those regions (Frost 2003; Ruff et al. 2006). Mechanical loading influences bone remodeling, but the degree and nature of this influence are not well appreciated. On the one hand, because gestation increases total body mass, we expect that weight-- bearing regions may be more affected by parity than non-weight-bearing regions. On the other hand, gestation and lactation draw critical

resources from the mother's bodily stores, including from bones (e.g., Prentice 2003; Prentice and Prentice 1988). Understanding if and to what extent parity affects BMD and if that influence varies by region may shed light on the role of mechanical loading in buffering some regions from systemic bone loss, if such an effect exists.

A recent study utilized data from the National Health and Nutrition Examination Survey (NHANES) to investigate associations between parity and BMD in the femoral neck and lumbar spines of postmenopausal women in the U.S. (Yang et al. 2022). While not exhaustive, the study exposed significant differences in parity-- BMD associations between these two anatomical regions. High parity (≥ 6 live births compared to 1–2 live births) was associated with low BMD in the lumbar spine but not the femoral neck, implying that differences in mechanical loading or bone type (e.g., trabecular vs. cortical) between the two regions may moderate high parity-BMD associations. Although the results of Yang et al. are suggestive, it is unclear if differences in loading profile or microarchitecture buffer some skeletal regions from net BMD loss resulting from acute or chronic somatic investment in reproduction. The aims of this study, therefore, are to investigate (1) if a relationship between parity and BMD exists among NHANES participants and (2) if so, to determine the extent to which that relationship differs across anatomical regions.

4.3 MATERIALS AND METHODS

4.3.1 Study Population

This study utilizes 2007–2018 cohort data from NHANES. This program collects demographic, socioeconomic, and health-related data from a nationally representative sample of approximately 5000 noninstitutionalized U.S.-living persons each year. Of the 70,000+ participants between

2007 and 2018, all those who identified as men and women without dual-energy x-ray absorptiometry (DXA) examination and reproductive data were excluded, as well as participants who had been diagnosed with or treated for osteoporosis. Participants were further excluded if they had been diagnosed with diabetes, emphysema, chronic bronchitis, thyroid, liver, or kidney disease, or cancer or malignancy of any kind, or met U.S. Centers for Disease Control and Prevention (CDC) adult standards for categorization as under- weight (BMI < 18.5 kg/m2) or severely obese (BMI > 40 kg/m2). Finally, participants were excluded from analyses if data on any included covariables were unavailable. After exclusions, 5144 non-pregnant, non-lactating women aged 20–79 were included in this study (see Table 1 for descriptive statistics; see Table S3 for details by region). The Ethics Review Board of the National Center for Health Statistics (NCHS) approved the survey protocols, and informed written consent was obtained from all participants.

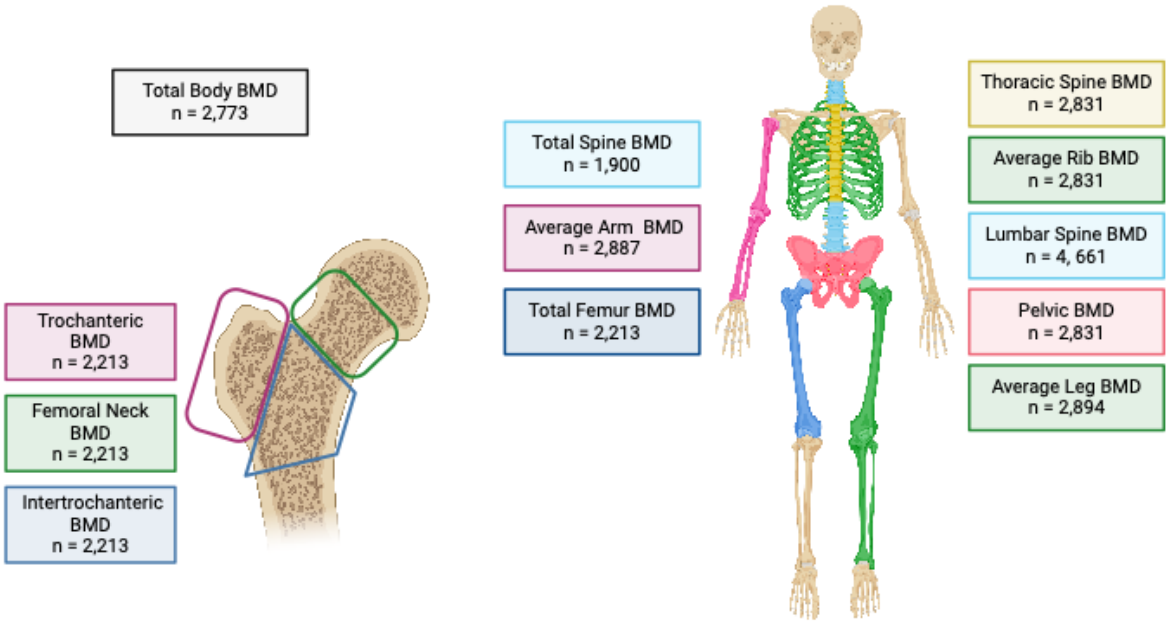

Figure 1: Diagram of regions with available dual-energy x-ray absorptiometry (DXA) data and respective participant counts. BMD = Bone Mineral Density.

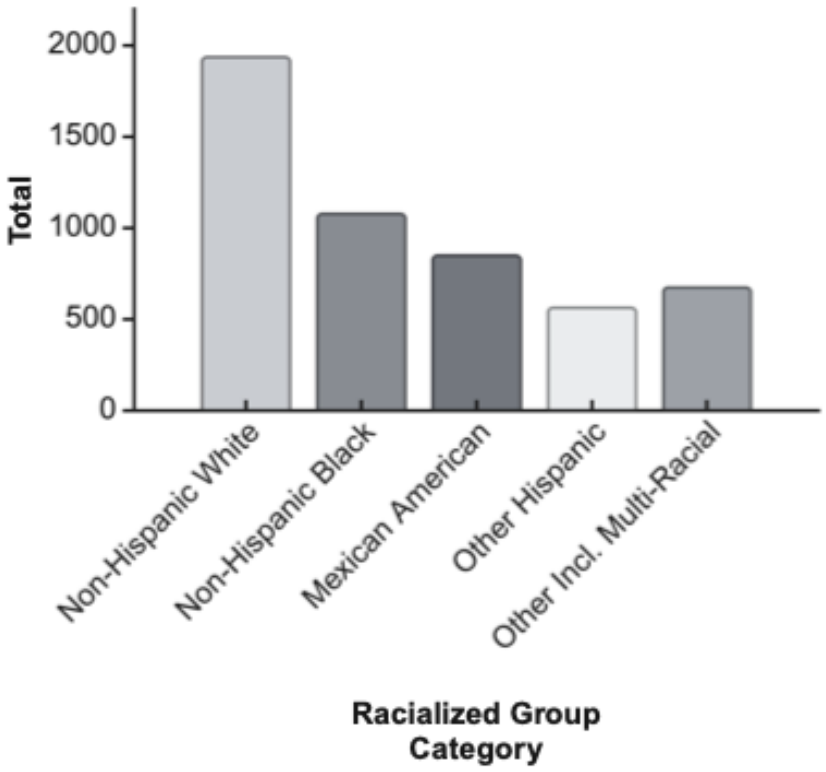

Figure 2. Histogram of participant count separated by racialized group.

4.3.2 Bone Mineral Density

BMD was measured by DXA, which measures BMD by spectral imaging proxy (i.e., optical density per square centimeter of bone surface) (Genant et al. 1996). DXA scans of 12 anatomical regions (Figure 1) were performed at the NHANES mobile examination center according to the manufacturer-recommended procedures for a QDR 4500A (2007–2010 cohorts) or Discovery A (2011–2018 cohorts) fan beam densitometers (Hologic Inc., Bedford, MA). These densitometers produce ionizing radiation in the form of x-- rays and use laser radiation to position scans. Scans

containing artifacts that could affect the accuracy of the DXA results, such as prosthetic devices, implants, or other extraneous objects, had the regional and global DXA results for these exams set to missing in the dataset (Center for Health Statistics 2018).

4.3.3 Parity

Parity, for the purposes of this study, is a participant's total number of deliveries (including stillbirths and live births). The total number of deliveries combines NHANES Reproductive Health Questionnaire (RHQ) values for the total number of cesarean and total number of vaginal deliveries. Participants with total delivery values above 11 were coded in NHANES as 11.

Table 1. Chapter 4 Descriptive Statistics

Table 1. Descriptive statistics of key variables.

Variable	Sample Mean or %	SD	Min	Max
Age in years	39.7	13.4	20.0	79.0
Number of Deliveries	1.8	1.6	0.0	11.0
Nulliparous	27.8%			
Mass (kg)	72.1	14.9	39.6	133.3
Height (cm)	161.4	7.0	135.3	187.8
BMI (kg/m^2)	27.7	5.3	18.5	39.9
Racialized Group				
Non-Hispanic White	37.8%			
Non-Hispanic Black	21.1%			
Mexican-American	16.7%			
Non-Hispanic Other	11.1%			
Other Incl. Multi-Racial	13.3%			
Highest Level of Education				
Less Than 9th Grade	6.4%			
9-11th Grade (Incl. 12th Grade w/ No Diploma)	11.8%			
High School Grad/GED or Equivalent	20.0%			
Some College or AA Degree	34.3%			
College Graduate or Above	27.6%			
Family Poverty Income Ratio				
<1.3 (low-income)	31.4%			
1.3-3.4 (middle-income)	37.2%			
3.5-5 (high-income)	31.4%			
Smoking Status				
Non-Smoker	72.3%			
Former Smoker	9.4%			
Current Smoker	11.1%			
Heavy Smoker	9.1%			
# Weekly Drinks	2.0	4.9	0.0	84.0
Lifetime Estrogen Exposure (years)	24.2	10.4	3.0	67.0
Age at Menarche (years)	12.7	1.7	6.0	21.0
Sedentary Hours/Day	5.8	3.4	0.5	20.0

4.3.4 Control Variables

Our control variables could influence parity, BMD, or their relationship but lie outside our hypothesized pathway of interest, that is, parity's effect on regional BMD. These variables included participant age, body mass index (BMI), self-reported racialized group identity, education level, family poverty income ratio (FPIR), smoking behavior, alcohol use, daily sedentary time, and reproductive health history (i.e., age at menarche, lifetime estrogen exposure), collected via NHANES questionnaires. Control variables were selected to explicitly

control for fundamental lifestyle differences that are shown to significantly impact or covary with BMD (e.g., mechanical loading Christen et al. 2014; Greene and Naughton 2006; Sugiyama et al. 2002), family poverty income ratio (Amiri et al. 2008; Navarro et al. 2009; Psaki et al. 2019), and alcohol use (Felson et al. 1995; Holbrook and Barrett-Connor 1993) in addition to age and BMI.

The participant's age in years was reported at the time of examination. BMI was reported as mass in kilograms divided by stature in square meters. Socioeconomic status and racialized group identity represent essential factors for reproductive, bone, and other health-- related outcomes, in part because their variation often correlates with differential access to health-protective resources, including, but not limited to, income and educational attainment (e.g., Amiri et al. 2008; Navarro et al. 2009; Psaki et al. 2019), adequate healthcare and nutrition (e.g., Baird et al. 2006; Ellison 2003), and differences in potential exposure to psychosocial stress (e.g., Grobman et al. 2018). As such, racialized grouping is based on participant self-identification with one of five categories provided by NHANES: Mexican American, Other Hispanic, Non-- Hispanic White, Non-Hispanic Black, or Other, which includes multi-racialized identities (Figure 3). Educational attainment is categorically defined as the highest level of education a participant completed at the time of the survey: less than 9th grade; 9-11th grade (includes 12th grade with no diploma); high school graduate/GED or equivalent; some college or A.A. degree, and college graduate or above. FPIR was calculated by dividing family (or individual) income by the geographically relevant U.S. Department of Health and Human Services poverty guidelines for the survey year. Smoking behavior was treated categorically and is divided into non-smokers (less than 100 cigarettes in a lifetime or quit smoking >15 years prior), former smokers (quit smoking <15 years prior), moderate (<0.5 pack/day), and heavy

smokers (≥ 0.5 pack/day). Alcohol use is measured by average weekly drinks over the most recent year.

Sedentary time was self-reported time spent sitting or reclining but not sleeping and was included to better characterize total weight-bearing and non-weight-bearing time without assuming the loading value of the reported physical activity. This is especially important for contextualizing BMD differences in the lumbar spine and lower limb regions. While this variable does not fully capture skeletal exposure to loading, the NHANES physical activity data collection protocol inspired a conservative approach to its measurement.

Reproductive health history was collected from RHQ and disease history questionnaires. Age at menarche was self-reported in years. Lifetime estrogen exposure was calculated using the total number of years between menarche and the most recent menstrual cycle, combined with the lifetime duration of HRT use, calculated as the total time, in years, a participant recalls having used estrogen-only, or estrogen-progesterone combination pills or patches (Rasgon et al., 2005).

4.3.5 Statistical Analyses

Using a series of multiple linear regression models, we tested for associations between parity and BMD in 12 measured regions: the legs, arms, and ribs, the total femur, femoral neck, greater trochanter, intertrochanteric region, the lumbar and thoracic spine regions, total spine, and total body. Model 1 is unadjusted and establishes the main effect of parity on BMD. Model 2 adjusts for age and BMI. Model 3 adjusts for age, BMI, racialized group, education level, FPIR, smoking behavior, number of weekly drinks, daily sedentary time, age at menarche, and lifetime estrogen exposure. If the coefficient associated with parity is reduced substantially when additional covariates are added, we interpret this as evidence that these covariates are at least

partially confounding or mediating the association of interest. Statistical significance for all three models was set at $p<0.004$, established by Bonferroni correction of an initial statistical significance of $p<0.05$. All analyses were performed in Stata 17.0.

4.4 RESULTS

In the unadjusted model (Model 1), parity is negatively associated with BMD in the lower limb: the total femur ($\beta = -0.008$; $p<0.001$) femoral neck ($\beta= -0.012$; $p<0.001$), trochanter ($\beta= -0.006$; $p<0.001$), intertrochanteric regions ($\beta = -0.007$; $p<0.001$), and average leg ($\beta= -0.005$; $p<0.001$), as well as in the lumbar ($\beta = - 0.008$; $p<0.001$) and total spine regions ($\beta= - 0.011$; $p<0.001$) and ribs ($\beta= -0.003$; $p<0.001$) In the arms, however, the association was *positive* ($\beta= 0.002$; $p<0.001$).

In Model 2, the association between parity and BMD is *positive* in total BMD ($\beta= 0.004$; $p=0.002$) and some non-weight bearing regions, specifically, arms ($\beta=2.653$ E-03; $p<0.001$) and pelvis ($\beta=10.106$ E-03; $p<0.001$), but *negative* in the legs ($\beta= -0.003$; $p=0.001$).

Model 3 is similar to Model 2, with positive associations in total BMD ($\beta=0.006$; $p<0.001$), the arms ($\beta=0.002$; $p=0.003$), and the pelvis ($\beta=0.008$; $p<0.001$) (Table 2).

Table 2. Parity-BMD Associations by Anatomical Region

Table 2. Parity-BMD associations by anatomical region

Anatomical Region	Total BMD	Total Femur	Total Spine	Lumbar Spine	Thoracic Spine	Femoral Neck	Trochanter	Intertrochanter	Avg Arm	Avg Leg	Avg Rib	Pelvis
Model 1 (Unadjusted)												
β	0.002	**-0.008***	**-0.011***	**-0.008***	0.001	**-0.012***	**-0.006***	**-0.007***	0.002	**-0.004***	**-0.003***	**0.005***
	(0.001)	(0.002)	(0.002)	(0.001)	(0.001)	(0.002)	(0.001)	(0.002)	(0.001)	(0.001)	(0.001)	(0.002)
p-value=	0.137	<0.001	<0.001	<0.001	0.482	<0.001	<0.001	<0.001	0.007	<0.001	<0.001	0.004
Observations	2,773	2,213	1,900	4,661	2,831	2,213	2,213	2,213	2,887	2,894	2,831	2,831
Model 2 (Age & BMI)												
β	**0.004***	0.001	-0.002	-0.000	0.001	0.001	-0.001	0.002	**0.003***	-0.003	0.000	**0.008***
	(0.001)	(0.002)	(0.002)	(0.001)	(0.001)	(0.002)	(0.001)	(0.002)	(0.001)	(0.001)	(0.001)	(0.002)
p-value=	0.001	0.711	0.391	0.946	0.325	0.383	0.466	0.4	0.001	0.022	0.692	<0.001
Observations	2,773	2,213	1,900	4,661	2,831	2,213	2,213	2,213	2,887	2,894	2,831	2,831
Model 3 (Maximally Adjusted)												
β	**0.006***	0.002	0.002	0.003	0.002	0.002	0.001	0.003	**0.002***	-0.000	-0.000	**0.008***
	(0.001)	(0.002)	(0.002)	(0.001)	(0.001)	(0.002)	(0.001)	(0.002)	(0.001)	(0.001)	(0.001)	(0.002)
p-value=	<0.001	0.263	0.23	0.027	0.274	0.238	0.52	0.205	0.003	0.715	0.634	<0.001
Observations	2,773	2,213	1,900	4,661	2,831	2,213	2,213	2,213	2,887	2,894	2,831	2,831

Standard errors in parentheses. ***p≤0.004**

4.5 DISCUSSION

Life history theory posits that greater energetic investment in reproduction could constrain available resources for somatic maintenance, including bone remodeling, potentially leading to reduced BMD despite other factors such as mechanical loading and physical activity (Kirkwood & Rose, 1991b). A more robust understanding of the relationships between BMD and reproductive strategies in modern humans could help explicate the sex bias in the prevalence of BMD-related disease and how we may have adapted to the competing pressures of reproduction and bone health throughout our evolutionary past (Madimenos, 2015b).

Here, we evaluated the hypothesis that increased reproductive effort, assessed by total parity, is associated with lower BMD using cross-sectional data from NHANES. In the unadjusted model, parity is negatively associated with BMD in most regions; more births are associated with decreased BMD. In the arms, however, the opposite is true. In adjusted models, however, the nature of this relationship changed when controlling for potential confounding variables such as age, BMI, socioeconomic status, and racialized identity. This change in the relationship between parity and BMD suggests that the environmental, behavioral, and temporal context surrounding pregnancy and childbirth may be more relevant for investigating long-term reproductive costs and their impacts on BMD and related health outcomes than parity alone. For example, in Model 3, the effect of racialized group identity, specifically for non-Hispanic blacks compared to non-Hispanic whites, was nearly ten times the effect of parity. NHANES reproductive history questionnaire omits or inconsistently collects data on important variables known to impact BMD and correlate strongly with parity, such as breastfeeding frequency and duration or interbirth interval, making it difficult to detect or measure the importance of variation in reproductive cost using only parity.

In Model 2, significant associations between parity and BMD change direction compared to Model 1 and become non-significant in some regions; notably, regions typically associated with higher mechanical strain and increased fracture risk with age (e.g., total femur, femoral neck, trochanter). Because bone remodeling is sensitive to mechanical loading and BMD increases through young adulthood, followed by a gradual decrease with age (J. A. Kanis et al., 1994), BMI and age should contextualize the association between parity and BMD. Overall, the change in the association between parity and BMD in this model indicates that parity may be moderated or confounded by age and BMI in the unadjusted Model 1. These results are consistent with a metanalysis (Song et al., 2017), which also found the association between parity and BMD to be site-specific and sensitive to age and BMI adjustment.

Model 3, like Model 2, yields similar effect sizes in the positive association between parity and BMD. This result is compatible with (Gur et al., 2003; Murphy et al., 1994; Sharma et al., 2016; Stieglitz et al., 2015b; Yang et al., 2022) but conflicts with (Lee, 2019; Specker & Binkley, 2005), but see (Song et al., 2017). This discrepancy may reflect the limitations of using parity as a proxy measure for lifetime reproductive cost. Beyond the number of pregnancies, the timing of key reproductive events (e.g., menarche, first birth, and menopause) is linked to variation in hormone-related health outcomes with age (InterLACE Study Team, 2019), suggesting that more complex interactions may also influence BMD. Definitions and measurements of the physiological costs of reproduction are as variable as the contexts in which reproduction occurs. Each pregnancy, successful parturition, and thus, increase in parity, requires a confluence of biological, behavioral, and environmental components whose dynamic influence on bone remodeling processes may be challenging to differentiate (Jasienska et al., 2017).

Model 3 explicitly controls for fundamental lifestyle differences that are shown to impact BMD (e.g., physical activity, socioeconomic status, drug and alcohol use) in addition to age and BMI; however, mechanical loading is not well controlled due to the information available in NHANES. Mechanical loading is dependent not only on body mass but also on the intensity and duration of physical activity (Gunter et al., 2012), and the bone deposition potential of mechanical loading is further dependent on nutrient availability (Ruff et al., 2006). For example, physical activity in nutritionally scarce environments could lead to higher energetic stress, accelerating resorption through increased nutrient demand.

Insufficient information exists in available NHANES data sets to understand the movement profiles of NHANES participants, although bipedal locomotion is assumed to be their predominant method of self-propulsion. We expect, therefore, that the mechanical loads in the femoral, lumbar, and leg regions are greater than those in other regions due to the biomechanical constraints of bipedalism and that these consistently applied loads might buffer weight-bearing regions from resorption. Consequently, weight-bearing regions may exhibit different relationships between parity and BMD than non-weight-bearing ones. For instance, weight-bearing regions could demonstrate a stronger relationship with parity than non-weight-bearing regions due to this potential buffering effect of consistent mechanical loading. We found that most weight-bearing regions (e.g., femoral neck, trochanter, intertrochanter, total femur) demonstrated no significant association between parity and BMD in Models 2 and 3 (but, see pelvis); however, non-weight-bearing regions (e.g., arms) show a positive relationship.

While higher physical activity levels in childhood and throughout adulthood are associated with increased BMD, particularly in weight-bearing regions (Borer, 2005; Pate et al., 2012), it is unclear whether this increases bone reserves, such that expected decreases from

pregnancy are less likely to lead to net BMD loss or if it impacts the rate at which bone is resorbed before, during, and following pregnancy (Gunter et al., 2012). Additional data is required to investigate the influence of mechanical loading on the association between BMD and reproductive variables.

These results indicate that reproductive costs and their subsequent impact on bone remodeling may not be well demonstrated by a simple proxy such as parity. Successful parturition and, therefore, increase in parity require a series of highly conserved biological processes that do not fully describe the variation in human reproductive histories or success. Likewise, BMD is only one measurement of bone health, and depending on the context, it is not necessarily the most informative. Changes in bone mineral density occur throughout an individual's lifespan and represent a confluence of factors that influence bone and overall somatic maintenance. Critical failure in bone's structural capacity for load bearing occurs when the net effect of deposition and resorption is insufficient resistance to excessive deformation. Given the consequences of that failure, compensatory mechanisms are likely variably effective at buffering humans against reproduction-related compromises in bone remodeling.

4.5.1 Limitations

Some limitations to this analysis should be noted. First, NHANES data are cross-sectional, and some cohorts contain inconsistent or incomplete data essential to investigating the relationship between reproductive costs and bone remodeling. For example, peak BMD is strongly associated with early childhood nutrition and skeletal loading, including growth patterns and physical activity levels (Gunter et al., 2012), comprehensive data for which is unavailable in NHANES.

The repeated nature of the survey, however, provides a sufficient sample (n=5,144) to allow interpretation of the results of these models with very narrow margins of error.

Second, NHANES biomarker data and reproductive health questionnaires are inconsistent, incomplete, or omit some biobehavioral variables relevant to bone remodeling, such as breastfeeding behavior (Bjørnerem et al., 2011; Hwang et al., 2016; Lee, 2019), birth control use (Crane et al., 2020; Lovett et al., 2017), endogenous hormone levels (Eriksen, 2010b), and chronic inflammation (Ginaldi et al., 2005; Mundy, 2007; Wallace, Worthington, et al., 2017).

NHANES data on diet and nutrition is inconsistent or temporally irrelevant for reasonably inferring nutritional status during critical periods for establishing bone growth patterns (Shams-White et al., 2017; Zhu & Prince, 2012). For instance, no consistent question(s) addressed calcium intake during juvenile bone development or in adulthood in the participants. Additional data is, therefore, required to investigate the influence of nutrition and mechanical loading on the association between BMD and reproductive variables.

Further, NHANES data describe participants' physical activity levels based on the estimated energetic costs of reported activities – not the expected impacts on the mechanical loading of the bone. We recognize that sedentary time does not fully capture bone exposure to loading; however, limited available data inspired a conservative approach to its measurement to avoid assuming the effect of differences in type or intensity of physical activity. For these reasons, the construction and inclusion of certain variables that may better contextualize lifetime bone metabolism or differences in reproductive history were not included. Future work would benefit from longitudinal data analyses and a more thorough exploration of the variation in lifetime estrogen exposure (e.g., multiple birth events, duration of breastfeeding, and type and duration of hormonal birth control use).

4.6 CONCLUSIONS

It is improbable that the human reproductive system evolved in an environment with infinite energetic resources to support pregnancy and infant growth (Dufour & Sauther, 2002a; Gittleman & Thompson, 1988; Jasienska et al., 2017). Consequently, human evolutionary fitness relies not only on successful gestation and parturition but also on other circumstances that place substantial physiological, psychosocial, and biomechanical stress on a mother. Any population-specific associations between parity and BMD may be highly sensitive to other reproduction-related variations such as the type and duration of birth control use, IBI, breastfeeding frequency and duration, nutritional status, and physical activity levels, regardless of the total number of offspring. Investigations into the cost of human reproduction and their underlying biocultural mechanisms should, therefore, include more holistic exposure variables and expand beyond simple parity measurements.

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Chapter 5: BONE MINERAL DENSITY VARIATION ACROSS ANATOMICAL REGIONS

Preface

This manuscript has been submitted for publication as an original article in the American Journal of Biological Anthropology under the title “Bone Mineral Density Variation Across Anatomical Regions: Insights from the National Health and Examination Survey” and authored by Cristina Gildee and Patricia Ann Kramer.

5.1 ABSTRACT

Objectives: Bone mineral density (BMD), a critical measurement of overall bone health, is sensitive to nutritional, hormonal, immunological, lifestyle, and genetic factors through their impact on bone remodeling and age-related BMD loss. Further, bone responds to repetitive mechanical loading by increasing bone mineral deposition, suggesting that differences in bone loading could moderate associations between age and BMD by buffering weight-bearing regions against age-related resorption. We examine whether age-BMD relationships differ across skeletal sites and between weight-bearing (WBR) and non-weight-bearing (non-WBR) regions.

Methods: Data from adult participants (n = 12,403) of the National Health and Nutrition Examination Survey (NHANES; 2007–2018) were analyzed using multivariate linear regression, adjusting for body mass index, gender, racialized group, socioeconomic status, smoking, alcohol consumption, and sedentary behavior. BMD was evaluated across 12 anatomical regions.

Results: WBR and non-WBRs showed similar age-related declines in BMD overall, though this pattern varied by gender. Women showed steeper age-related BMD decline in non-WBRs; men showed comparable negative associations between regions. Non-Hispanic Black participants had significantly higher BMD in every region than non-Hispanic White participants. Socioeconomic status and heavy smoking were strong predictors of BMD. Notably, increased sedentary time was linked exclusively to lower BMD in non-WBRs (all $p<0.001$).
Discussion: These results indicate habitual loading alone may be insufficient to buffer bones against age-related loss. Rather, social and lifestyle factors significantly moderate the age-BMD relationship. Further research employing longitudinal data, direct mechanical loading measurements, and bone microarchitecture assessments could help clarify the interplay of biomechanical and social factors influencing BMD.

5.2 INTRODUCTION

Bone mineral density (BMD), a critical measure of bone health, is regulated by a highly conserved and dynamic bone remodeling process involving the concurrent deposition and resorption of bony matrix (Hadjidakis & Androulakis, 2006). In humans, BMD typically increases during childhood and peaks in early adulthood before gradually decreasing with age (Berger et al., 2010; Demontiero et al., 2012; Hendrickx et al., 2015). Age-related BMD loss contributes to an increased risk of fractures and other skeletal morbidities (Raisz 2005; Burr et al. 1997; Riggs and Melton 1995; Cauley 2013; Kanis 2002); therefore, understanding the factors that influence age-related changes in BMD is essential for developing effective strategies to maintain bone health across the lifespan. Various factors, including genetics (Estrada et al., 2012; Greenhill, 2019; Morris et al., 2019), hormone fluctuations (Ettinger et al., 1985; Kameda

et al., 1997; Nguyen et al., 1995; Petitti et al., 2000), nutritional status (Warren, 2011), immune function (Lian et al., 2011b; Tang et al., 2022), and lifestyle (Kanis et al. 2005; Jensen, Christiansen, and Rødbro 1985; Felson et al. 1995; Berg et al. 2008; Gunter, Almstedt, and Janz 2012), have been shown to influence the remodeling process.

Further, bone remodeling is sensitive to mechanical stimuli (Ehrlich & Lanyon, 2002; Frost, 2003b; Greene & Naughton, 2006; Wallace, Demes, et al., 2017). Skeletal regions are subjected to differential exposure to external (e.g., ground reaction) and internal (e.g., muscle) forces as individuals engage in their daily activities (Fluit et al., 2014). The direction, magnitude, and frequency of these forces substantially impact the development, morphology, microarchitecture, and density of the bone tissue (Hadjidakis & Androulakis, 2006; Ruff et al., 2006). The specific loading patterns experienced by different skeletal regions are expected to lead to variations in BMD within and between anatomical sites as bone adapts to mechanical stress (Frost, 2001; 2003). For example, skeletal regions that are more highly loaded during weight-bearing activities, such as the lower limbs, tend to exhibit different microarchitecture of the bony matrix to resist excessive deformation or potential structural failure than those that experience lower loads, such as the upper limbs (Amling et al., 1996; Chirchir et al., 2015). These adaptations are critical to ensuring the structural integrity of the bone, allowing it to withstand the mechanical forces encountered during daily activities, including walking, running, and lifting (Ehrlich & Lanyon, 2002; Greene & Naughton, 2006; Ruff et al., 2006; Sugiyama et al., 2002).

The relationship between mechanical loading and bone remodeling is complex, and while loading influences bone deposition, the precise mechanisms by which this occurs are not fully understood. The extent of bone adaptation to mechanical stimuli varies based on factors such as

the type of loading (e.g., compression, tension, shear), the frequency and duration of the loading, and the physiological capacity to synthesize the necessary materials to produce the bony matrix (Ruff et al., 2006; Wallace, Demes, et al., 2017). Individual characteristics such as nutritional status, genetics, physical activity levels, and endogenous hormone exposure modulate how bones respond to mechanical stress (Hadjidakis and Androulakis 2006; Eriksen 2010). Variations in these factors make it challenging to predict how mechanical loading affects BMD among individuals over time. Further, it is unclear if the relationship between mechanical loading and bone deposition confers a differential advantage across anatomical regions or if all regions are equally vulnerable to BMD loss with age, regardless of mechanical loading profile.

Here, we examine whether weight-bearing regions (WBRs) of the skeleton, which are subjected to repetitive mechanical forces during activities such as standing and bipedal locomotion, are less susceptible to the effects of age-related BMD changes than non-weight-bearing regions (non-WBRs), which do not experience the same repetitive mechanical loading. We use anatomical region as a proxy for mechanical loading to distinguish the specific contribution of loading from other factors influencing bone health. Further, we investigate how differences in lifestyle variables – such as physical activity, smoking habits, and sedentary behavior – confound or moderate the relationship between BMD and age to better characterize their influence on age-related decreases in BMD.

We leverage the power of a large population-specific dataset, the National Health and Nutrition Examination Survey (NHANES), to examine these relationships. The U.S. Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS) funds and facilitates the NHANES program, which has continuously collected clinical examinations, selected medical and laboratory tests, and self-reported surveys from approximately 5,000

children and adults each year since 1999. NHANES participants are a nationally representative sample of the U.S. civilian non-institutionalized population; their data is deidentified and made publicly available in 2-year cycles. NHANES data is regularly used to assess trends in U.S. health and disease prevalence, to drive public health policy, and to direct health care services nationally.

5.3 MATERIALS AND METHODS

5.3.1 Study Population

Of the more than 70,000 NHANES participants between 2007 and 2018, those without dual-energy X-ray absorptiometry examination data or missing data for covariates were excluded. Also excluded were participants whose height and mass measurements met CDC categorization criteria as severely obese (body mass index, or BMI ≥ 40) or underweight (BMI ≥ 18.5) and all those who had been diagnosed with diabetes, emphysema, chronic bronchitis, thyroid, liver, or kidney disease, or cancer or malignancy of any kind, as these conditions can affect BMD. After these exclusions, 12,403 Participants aged 20-79 were included in this study. (See Table 1 for descriptive statistics.) The Ethics Review Board of the National Center for Health Statistics (NCHS) approved the NHANES survey protocols and informed written consent was obtained from all participants.

5.3.2 Bone Mineral Density

Dual-energy X-ray absorptiometry (DXA) was used to measure BMD at multiple skeletal sites in participants of the NHANES. DXA is considered the gold standard for BMD assessment due to its high precision (typical in vivo coefficient of variation <1%) and low radiation dose (~1-5 μSv per scan). Compared to earlier absorptiometry methods, DXA offers superior reliability and

cross-site standardization. Its high resolution and areal density output enable accurate cortical and trabecular bone assessment across sites, though it does not provide volumetric density (Genant et al. 1996; Bazzocchi et al. 2016; Alawi et al. 2021).

DXA scans were conducted by trained technicians in mobile examination centers, following standardized protocols established by the NCHS. Whole-body and regional BMD data were collected using a QDR 4500A (2007-2010 cohorts) or Discovery A (2011-2018 cohorts) fan beam densitometers (Hologic, Inc., Bedford, MA). Daily calibration, system performance checks, and quality control scans were performed using anthropomorphic phantoms, and trained analysts reviewed and processed raw scan files using manufacturer-specific software with automated edge detection and segmentation protocols. Participants were scanned while lying supine, with limbs positioned using standardized supports to minimize movement and optimize reproducibility. Those scans containing artifacts that could affect the accuracy of the DXA results, such as prosthetic devices, implants, anatomical anomalies, or other extraneous objects, had the regional and global DXA results for these exams set to missing in the dataset (Center for Health Statistics 2016). Further details of the DXA examination protocol are documented in the Body Composition Procedures Manual on the NHANES website.

DXA measurements included whole-body, lumbar spine, proximal femur (including femoral neck, trochanter, and intertrochanteric regions), arms, ribs, pelvis, and legs. We selected these anatomical sites to capture both weight-bearing and non-weight-bearing regions, providing insights into the skeletal effects of mechanical loading and systemic influences. Total leg BMD is used as a proxy for weight-bearing regions (WBR), while arm and rib BMD represent non-weight-bearing regions (non-WBR).

5.3.3 Control Variables

We include control variables that could influence BMD but lie outside our hypothesized pathway of interest, i.e., the effect of age on regional BMD. Collected via NHANES questionnaires, control variables include participant gender, self-reported racialized group identity, BMI, education level, family poverty income ratio (FPIR), smoking behavior, alcohol use, and daily sedentary time. Control variables are selected to explicitly control for fundamental lifestyle differences that have been shown to significantly impact or covary with BMD (e.g., mechanical loading (Christen et al. 2014; Greene and Naughton 2006; Sugiyama, Yamaguchi, and Kawai 2002), family poverty income ratio (Amiri et al. 2008; Navarro et al. 2009; Psaki et al. 2019), and alcohol use (Felson et al. 1995; Berg et al. 2008; Holbrook and Barrett-Connor 1993) in addition to age and BMI.

The participant's age in years was reported at the time of examination. BMI was calculated as mass in kilograms divided by stature in square meters. Socioeconomic status and racialized group identity represent essential factors influencing aging bone and other health-related outcomes, in part because their variation often correlates with differential access to health-protective resources. Influential resources include but are not limited to, income and education (e.g., Amiri et al., 2008; Gur et al., 2004; Navarro et al., 2009), adequate healthcare and nutrition (e.g., Brennan et al., 2011; McMaughan et al., 2020), and differences in potential exposure to psychosocial stress and their consequences (e.g., Cohen et al., 2007; Ng & Chin, 2021; Wu et al., 2009).

Racialized grouping categories are derived from the NHANES survey data collection protocol for the "RIDRETH1" variable. Participant grouping was determined by self-identification into one of five categories: Mexican American, Other Hispanic, Non-Hispanic

White, Non-Hispanic Black, and Other, including multi-racialized identities. Respondents who self-identified as “Mexican American” were coded as such in NHANES, regardless of their other race-ethnicity identities. Otherwise, self-identified “Hispanic” ethnicity results in categorization as “Other Hispanic.” All other non-Hispanic participants were then categorized based on their self-reported racialized grouping, as noted above.

Educational attainment was categorically defined as the highest level of education a participant completed at the time of the survey as follows: less than 9th grade; 9-11th grade (includes 12th grade with no diploma); high school graduate/GED or equivalent; some college or A.A. degree, and college graduate or above. FPIR in this study is derived from the NHANES “INDFMPIR” variable, an index (0-5) for the ratio of family income to poverty that was calculated by dividing family (or individual where relevant) income by geographically pertinent U.S. Department of Health and Human Services poverty thresholds for each survey year. NHANES top codes this variable at five because of disclosure concerns.

Smoking behavior and alcohol use are calculated based on participant responses to “SMQ” and “ALQ” questionnaires, respectively. Smoking behavior is divided into four categories: non-smokers (less than 100 cigarettes in a lifetime or quit smoking >15 years prior), former smokers (quit smoking <15 years prior), moderate (<0.5 pack/day), and heavy smokers ($\geq$ 0.5 pack/day). Alcohol use is calculated as the average weekly drinks consumed using responses to questions about frequency and number of drinks per drinking event over the most recent year.

Sedentary time was the self-reported time spent sitting or reclining (but not sleeping) and is included to better characterize total weight-bearing and non-weight-bearing time without assuming the loading value of the reported physical activity. This is especially important for

contextualizing BMD differences in the lumbar spine and lower limb regions. While this variable does not fully capture skeletal exposure to loading, the NHANES physical activity data collection protocol inspired a conservative approach to its measurement.

5.3.4 Statistical Analyses

48,551 DXA scans provide the BMD measurements from which z-scores are calculated for each participant, either over the entire sample or stratified by gender, depending on the analytic grouping. Using multiple linear regression models, we test whether the association between age and BMD is different between men and women in 12 measured regions: the legs, arms, ribs, total femur, femoral neck, greater trochanter, intertrochanteric region, the lumbar and thoracic spine regions, total spine, and total body. Total leg BMD is used as a proxy for WBR because the femur and tibia are exposed to substantial mechanical loading during daily activities like walking and standing. These regions are key in supporting total body mass during bipedal locomotion. In contrast, the lumbar spine, although involved in weight-bearing, is subject to a different set of biomechanical stresses and is also influenced by factors like posture and spinal loading and activities such as sitting, which can vary substantially among people. The arms and ribs do not support body weight during typical activities like walking or standing; thus, individuals could substantially vary in the regular mechanical loading of the arms. We use the BMD of the arms and ribs as a proxy for non-WBR.

Control variables include BMI, the interaction between age and gender, racialized group, education level, FPIR, smoking behavior, number of weekly drinks, and daily sedentary time. This model was then applied separately to women and men as subgroups to explore gendered differences in regional age-BMD associations. In gender-restricted sample analyses, related interaction and variables are removed. Statistical significance for all models is set at $p<0.004$,

established by Bonferroni correction of an initial statistical significance of $p<0.05$. All analyses are performed in Stata 18 SE.

5.4 RESULTS

5.4.1 Descriptive statistics

Descriptive statistics for the study population are presented in Table 3. After applying our exclusion criteria, the final analytical sample included 12,403 adults aged 20–79 (mean age: 39.6 years). Women comprise 45.9% of the sample and had significantly lower BMD than men across all regions except for the total, lumbar, and thoracic spine, where they had higher BMD (all $p \leq 0.004$). Non-Hispanic Black participants have higher BMD than non-Hispanic White participants in all regions ($p<0.001$), independent of age, BMI, or lifestyle factors. This difference is most pronounced in the ribs. Conversely, all other racialized groups demonstrate lower BMD across most regions, although this difference did not always reach statistical significance. Mean BMI was 27.6 ± 5 kg/m² and is positively associated with BMD ($p< 0.001$).

Table 3. Chapter 5 Descriptive Statistics

Variable	Sample Mean or %	SD	Min	Max	Women's Mean or %	SD	Min	Max	Men's Mean or %	SD	Min	Max
Age in years	39.6	13.4	20.0	79.0	39.8	13.4	20.0	79.0	39.5	13.3	20.0	79.0
Gender					45.9%				54.1%			
Mass (kg)	78.8	16.8	39.2	144.4	72.0	15.0	39.6	133.3	84.6	16.1	39.2	144.4
Height (cm)	168.6	10.0	135.3	203.8	161.3	7.0	135.3	187.8	174.8	7.7	136.5	203.8
BMI (kg/m^2)	27.6	5.0	18.5	40.0	27.7	5.3	18.5	39.9	27.6	4.6	18.5	40.0
Racialized Group												
Non-Hispanic White	38.3%				17.0%				21.3%			
Non-Hispanic Black	21.0%				9.7%				11.4%			
Mexican-American	16.3%				7.7%				8.6%			
Non-Hispanic Other	10.3%				5.1%				5.2%			
Other Incl. Multi-Racial	14.1%				6.5%				7.6%			
Highest Level of Education												
Less Than 9th Grade	7.5%				3.2%				4.2%			
9-11th Grade (Incl. 12th Grade w/ No Diploma)	13.0%				5.4%				7.6%			
High School Grad/GED or Equivalent	22.6%				9.1%				13.5%			
Some College or AA Degree	30.6%				15.5%				15.1%			
College Graduate or Above	26.3%				12.6%				13.6%			
Family Poverty Income Ratio												
<1.3 (low-income)	31.5%				14.7%				16.7%			
1.3-3.4 (middle-income)	36.8%				17.0%				19.8%			
3.5-5 (high-income)	31.7%				14.2%				17.6%			
Smoking Status												
Non-Smoker	64.3%				33.4%				30.8%			
Former Smoker	12.1%				4.2%				7.8%			
Current Smoker	11.5%				4.2%				7.4%			
Heavy Smoker	12.1%				4.1%				8.0%			
# Weekly Drinks	3.5	6.9	0	70	1.9	4.3	0	66	4.9	8.3	0	70
Sedentary Hours/Day	5.8	3.4	0.5	20	5.8	3.4	0.5	20	5.8	3.4	0.5	20

5.4.2 Associations between age and BMD

In the total sample, all anatomical regions show a significant negative relationship between age and BMD ($p<0.001$). Among these, total femur and femoral neck z-scores exhibit the largest effect ($\beta = -0.020$ and $\beta = -0.028$, respectively), indicating the most pronounced age-related BMD decline in these regions. In contrast, total BMD, thoracic spine, and average arm

regions demonstrate the smallest effect with age (β = -0.009, β = -0.006, and β = -0.007, respectively).

Contrary to our expectation, WBRs and non-WBRs exhibit similarly negative associations with age in the total sample with overlapping standard errors (See Table 2; WBR: β = −0.011, SE = 0.001; non-WBR: β = −0.012, SE = 0.001; both p<0.001); however, this pattern differs by gender. Women show steeper age-related declines in non-WBRs (β = −0.016) than WBRs (β = −0.013), while in men, WBRs decline similarly with age (β = −0.008) compared to non-WBRs (β = −0.007).

Table 4. Chapter 5 - Age and Regional BMD Associations.

Anatomical Region	Weight-Bearing	Non-WeightBearing	Total BMD	Total Femur	Total Spine	Lumbar Spine	Thoracic Spine	Femoral Neck	Trochanter	Intertrochanter	Avg Arm	Avg Leg	Avg Rib	Pelvis
Total Sample														
β for Age	**-0.011***	**-0.012***	**-0.009***	**-0.020***	**-0.018***	**-0.015***	**-0.006***	**-0.028***	**-0.017***	**-0.018***	**-0.007***	**-0.011***	**-0.017***	**-0.012***
	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
p=	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Observations	6,414	6,315	6,222	5,020	4,215	10,602	6,548	5,020	5,020	5,020	6,534	6,414	6,548	6,548
Women Only														
β for Age	**-0.013***	**-0.016***	**-0.010***	**-0.022***	**-0.020***	**-0.017***	**-0.006***	**-0.030***	**-0.019***	**-0.020***	**-0.009***	**-0.013***	**-0.021***	**-0.013***
	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
p=	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Observations	2,935	2,785	2,814	2,278	1,959	4,762	2,874	2,278	2,278	2,278	2,931	2,935	2,874	2,874
Men Only														
β for Age	**-0.008***	**-0.007***	**-0.006***	**-0.015***	-0.001	**-0.002***	**0.007***	**-0.026***	**-0.010***	**-0.013***	-0.002	**-0.008***	**-0.014***	**-0.009***
	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
p=	<0.001	<0.001	<0.001	<0.001	0.132	0.003	<0.001	<0.001	<0.001	<0.001	0.057	<0.001	<0.001	<0.001
Observations	3,479	3,530	3,408	2,742	2,256	5,840	3,674	2,742	2,742	2,742	3,603	3,479	3,674	3,674

Standard errors in parentheses. ***indicates significance (p≤0.004)**

5.4.3 Lifestyle and Socioeconomic Associations with BMD

Although secondary to our main objectives, the associations between our control variables and regional BMD are notable (see appendix C). The mean sedentary time was 5.76 ± 3.43 hours/day and was associated with lower BMD in non-WBR (β = −0.011; p<0.001) but not WBR. Across regions, sedentary time is negatively associated with Total BMD (β = −0.007; p<0.001), Thoracic Spine (β = −0.008; p = 0.002), Average Arm (β = −0.011; p<0.001), and Average Rib BMD (β = −0.009; p<0.001). Compared to non-smokers, heavy smokers (≥0.5

pack/day) have lower BMD in each of the femoral measurements (e.g., femoral neck: β = −0.099, p = 0.003) but higher BMD in the arms (β = 0.111, p<0.001).

Our socioeconomic status proxies are positively associated with higher BMD across regions. Higher FPIR is associated with higher BMD in both WBRs (β = 0.032, p<0.001) and non-WBRs (β = 0.023, p<0.001). Higher educational attainment is associated with higher BMD in WBRs (β = 0.164, p<0.001), total BMD (β = 0.166 for college graduates vs. <9th grade; p<0.001), and the lumbar spine (β = 0.16; p<0.001) but not in non-WBRs. These associations with lifestyle and socioeconomic measures are largely replicated in gender-based subsamples.

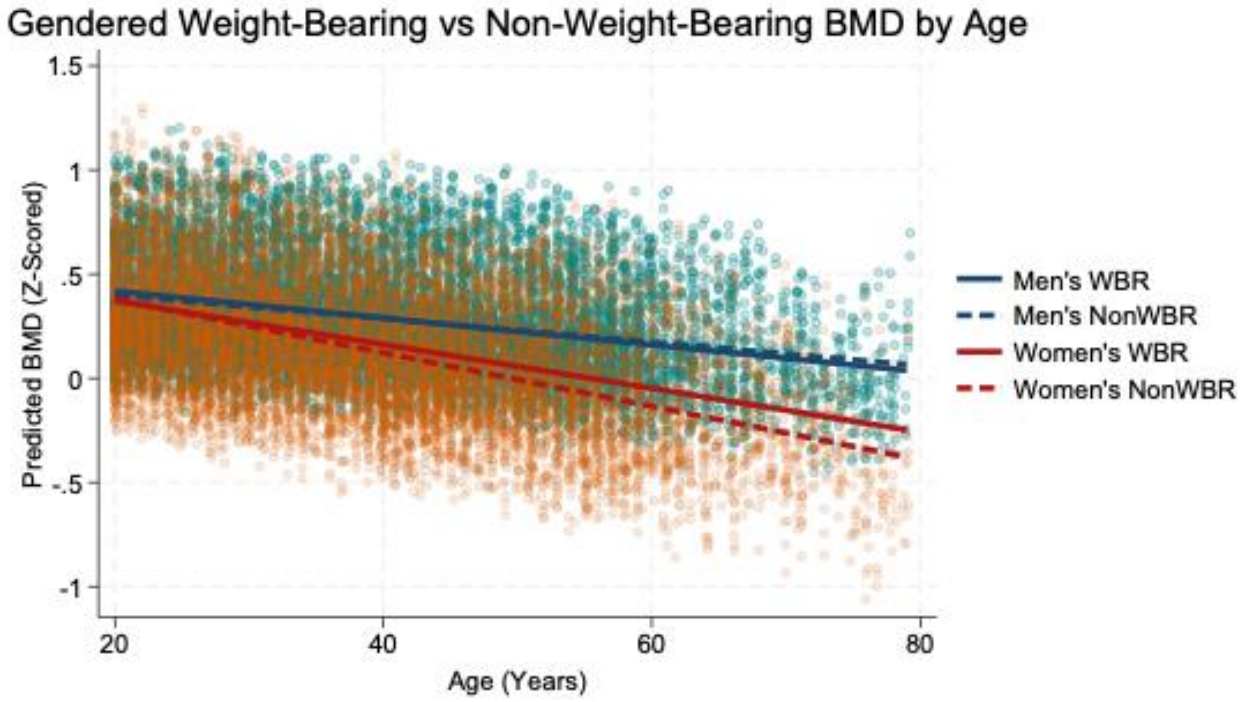

Figure 3. Predicted Weight-Bearing Region and Non-Weight-Bearing Regions by Age and Gender

5.5 DISCUSSION

Our analyses investigate the complex associations between age, BMD, and demographic and lifestyle factors across skeletal and between weight-bearing and non-weight-bearing regions

using NHANES data from a large U.S. adult population. We expected that skeletal regions that were weight-bearing (WBRs), that is, regularly subjected to the mechanical loads induced by walking and standing, would exhibit weaker age-related declines in BMD than non-weight-bearing regions (non-WBRs) due to the effects of habitual mechanical stimulation. Contrary to our expectation, we find that WBRs experienced similar or even greater age-related BMD declines than non-WBRs. This suggests that mechanical loading alone is insufficient to protect against age-related bone loss and that other underlying factors likely contribute to regional differences in BMD aging. Bone microarchitecture and cumulative bone damage are two factors that deserve more consideration. BMD (a measurement of areal bone mineral density) captures only a portion of total bone strength; however, the microarchitectural features of the bony matrix (i.e., trabecular connectivity; cortical thickness) also play a crucial role in bone's functional adaptations independent of BMD (Brandi 2009).

Bone microarchitecture necessarily varies across anatomical regions, with some areas (e.g., the greater trochanter and lumbar regions) exhibiting higher trabecular bone volume to reinforce these areas against excessive deformation under repetitive exposure to mechanical loading by transferring forces from the articular surface to cortical shell. This is especially important in vertebral bodies, where trabeculae are the primary load-bearing structure (Oftadeh et al. 2015; Chevalier, Pahr, and Zysset 2009; Chirchir et al. 2015). Despite its adaptive advantages in these regions, trabecular bone is particularly vulnerable to age-related degeneration because of its high surface area and unique architectural features: interconnected plates and rods that form the load-diffusing matrix and compress to function as critical shock absorbers within the bone(Stauber and Müller 2006). These elements may become thinner and

more disconnected with age, reducing their capacity to adapt to strain (Galassi et al. 2024; Eriksen 1986; Burr et al. 1985).

Notably, trabeculae also provide a greater surface area upon which remodeling can occur, resulting in comparatively increased remodeling activity. While remodeling helps maintain bone integrity, it may also expose WBRs to age-related degradation if remodeling within the trabeculae fails to maintain structural integrity or if resorption outpaces deposition due to hormonal shifts or cellular senescence. That is, the adaptive response of bone in WBRs may risk accelerated turnover-related bone loss in older age, and net BMD loss could occur despite the initial mechanical advantage of the remodeling (Burr et al. 1985). This mechanism could explain why WBRs in our study did not show better BMD preservation than non-weight-bearing regions. Although speculative, this possibility highlights the need for research incorporating direct measures of bone microarchitecture (e.g., trabecular bone scores or high-resolution 3D imaging) to confirm these regional differences and their role in BMD decline with age.

Further research would also benefit from access to data with better details on physical activity profiles. For instance, we could not distinguish among NHANES participants whose non-sedentary time was filled with activities that load the lower limbs with high forces (e.g., running, carrying heavy loads) from those with activities that load the lower limbs infrequently (e.g., swimming) and/or with low forces (e.g., walking slowly). Thus, we could not assess or control for variation in regional mechanical loading exposure in duration or intensity.

In gender-stratified analyses, women showed a steeper age-related decline in BMD across nearly all skeletal regions than men. This observation is consistent with well-established research and clinical practice identifying menopause-related estrogen declines and subsequent increases in bone resorption activity as significant risk factors for osteoporosis in women (Khosla, Oursler,

and Monroe 2012; Ettinger, Genant, and Cann 1985; Kameda et al. 1997; Popat et al. 2009; Cauley et al. 2003). Also, consistent with previous work on bone health, racialized group differences in BMD were observed, with non-Hispanic Black individuals demonstrating consistently higher BMD compared to non-Hispanic White individuals across skeletal regions (Araujo et al. 2007; Taaffe et al. 2001; Noel, Santos, and Wright 2021; Henry and Eastell 2000; Barrett-Connor et al. 2005; Cauley et al. 2005; Luckey et al. 1989; Ettinger et al. 1997; Kleerekoper et al. 1994).

Our results also demonstrate that the effect of lifestyle and socioeconomic factors is strong relative to the effect of age on regional BMD. Specifically, the negative effect of heavy smoking (compared to non-smokers) was up to nine times stronger than the negative effect of a one-year increase in age on BMD in highly loaded skeletal sites (e.g., trochanter: $\beta = -0.187$ and $\beta = -0.017$, respectively), consistent with prior studies suggesting tobacco exposure accelerates bone resorption and impairs bone formation via oxidative stress and inflammatory pathways (Kanis et al. 2005; Zhu et al. 2023; Ward and Klesges 2001). In contrast, socioeconomic measures, including educational attainment and FPIR, exhibited positive associations with regional BMD. Higher socioeconomic status may reflect improved access to nutritional resources, healthcare (including early osteoporosis screening or interventions), and physical activity opportunities, thereby leading to higher BMD across WBRs and non-WBRs, as seen here. Further analyses could investigate whether these factors could mitigate some aging effects on BMD, particularly in load-bearing regions. If true, this would provide an important avenue through which social advantages and disadvantages translate into BMD maintenance with age and bone health disparities between groups.

5.5.1 Limitations

Some limitations to this analysis should be noted. First, NHANES data are cross-sectional, restricting our ability to make causal inferences about the relationship between age and bone remodeling. Second, NHANES biomarker and questionnaire data are inconsistent, incomplete, or omit some biobehavioral variables key to BMD accrual throughout the life course, such as early childhood nutrition and chronic inflammation.

Further, NHANES data describe participants' physical activity levels based on the estimated energetic costs of reported activities, not the expected impacts on the mechanical loading of the bone. We recognize that sedentary time does not fully capture bone exposure to loading; however, limited available data inspired a conservative approach to its measurement to avoid assuming the effect of differences in type or intensity of physical activity. For these reasons, we could not include certain variables that could provide a more comprehensive understanding of lifetime mechanical loading exposures on bone.

Future research would benefit from the use of longitudinal data as well as the inclusion of early-life nutrition and physical activity data. Incorporating more granular data on mechanical loading, relevant genetic markers, inflammatory biomarkers, and other contextual lifestyle variables may provide a more nuanced picture of the complex mechanisms driving bone health across the lifespan.

5.6 CONCLUSION

Our results provide valuable insights into the complex interplay between aging, mechanical loading, demographic variables, and lifestyle factors influencing BMD. Contrary to our expectations, WBRs did not demonstrate protection against age-related declines compared to

non-WBRs; however, in the absence of data that allow us to fully control for physical activity or mechanical loading, we interpret our findings with caution and refrain from rejecting clinical recommendations that appropriate mechanical loading can mitigate bone loss.

Notable differences in BMD between racialized groups further highlight the need for tailored interventions addressing health disparities that consider the interactions between genetic variation, environmental conditions, and socioeconomic factors. Further, our results support previous work suggesting that demographic and behavioral factors, including gender, smoking habits, and SES, strongly influence BMD. Heavy smokers exhibited markedly lower BMD, while higher SES correlated positively with bone health, especially for load-bearing skeletal sites. Our analysis supports previous work arguing against overly simplistic biomechanical interpretations, suggesting that bone adaptation integrates lifelong mechanical, biological, and social determinants (Ruff, Holt, and Trinkaus 2006; Gildee and Kramer 2025).

Future research should build upon this analysis by investigating similar models in underrepresented populations in biomedical research, particularly those in non-WEIRD (Western, Educated, Industrialized, Rich, and Democratic) environments, and exploring culturally-specific influences on BMD such as reproductive history, life-long physical activity differences (e.g., office worker vs. agricultural laborers or professional athletes), dietary patterns, environmental exposures, and healthcare access, to provide a deeper understanding of how bone aging and related diseases are experienced globally.

Additionally, future studies should include longitudinal data, more comprehensive physical activity data, bone microarchitecture metrics, and molecular and other biological markers to help clarify the mechanisms underlying these relationships. More detailed data could

clarify if microarchitectural deterioration precedes measurable BMD declines, potentially providing early indicators of osteoporosis risk beyond standard DXA screenings.

Finally, our work stresses the importance of utilizing comprehensive biomechanical, demographic, and lifestyle-specific models to address disparities in bone aging outcomes, as well as the need to expand this research to include global populations with culturally specific developmental and aging contexts to improve strategies to mitigate bone loss and reduce fracture risks, particularly among vulnerable populations.

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Chapter 6: TELOMERE LENGTH AND BONE MINERAL DENSITY: Demographic and Reproductive Influences

6.1 INTRODUCTION

6.1.1 Skeletal Aging and Cellular Senescence

Bone's extraordinary material properties and ability to adapt rely on its ability to remodel continuously over the life course. In healthy bone, this process is tightly regulated to maintain skeletal integrity; however, with advanced age, resorption and deposition processes become uncoupled and imbalanced, leading to a net decline in bone mass and quality. Beyond (and distinct from) well-known factors like hormonal changes (e.g., postmenopausal estrogen withdrawal) and reduced mechanical loading (as sedentary time increases with age), cellular aging (e.g., cumulative DNA damage and cellular senescence) compromises bone's ability to maintain itself (Farr et al., 2019; Ginaldi et al., 2005; Pignolo et al., 2021).

Skeletal aging reflects a gradual imbalance in bone remodeling driven by both intrinsic cellular processes and external stressors. A key contributor to this imbalance is cellular senescence: a permanent state of cell cycle arrest that occurs in response to accumulated stressors such as DNA damage, oxidative stress, telomere attrition, and oncogenic signaling (Yousefzadeh et al., 2021). While senescent cells no longer divide, they remain metabolically active and adopt a distinct secretory profile known as the senescence-associated secretory phenotype (SASP). This profile includes elevated pro-inflammatory cytokines (e.g., IL-6, IL-1β), chemokines, matrix metalloproteinases, and other signaling molecules that propagate inflammation and tissue dysfunction (Ginaldi et al., 2005; Wrona et al., 2024).

In bone, cellular senescence affects several resident cell populations, including osteoblasts, osteocytes, and mesenchymal progenitor cells. Studies in rodent models and human

tissue have shown that senescent osteocytes accumulate with age and actively secrete SASP factors, which disrupt the delicate balance of bone remodeling by promoting osteoclastogenesis and impairing osteoblast differentiation and function (Farr et al., 2019; Manolagas, 2000; Pignolo et al., 2021). This leads to increased bone resorption and decreased bone formation, contributing to structural deterioration and osteoporosis (Ginaldi et al., 2005). The SASP also exerts paracrine effects, inducing secondary senescence in neighboring cells and amplifying skeletal dysfunction (Chandra & Rajawat, 2021).

Cellular senescence is typically initiated by sustained activation of the DNA damage response (DDR), a highly conserved signaling cascade involving sensor kinases such as ATM and ATR. These proteins phosphorylate downstream targets, such as p53 and CHK1/2, triggering transcriptional programs that upregulate tumor suppressors p21^CIP1^ and p16^INK4a^, key enforcers of cell cycle arrest. Concurrently, persistent DDR signaling activates transcription factors such as NF-κB and C/EBPβ, which drive the expression of SASP components. Although cellular senescence likely evolved as a tumor-suppressive mechanism, its chronic presence in aged tissues, including bone, promotes a pro-inflammatory state that compromises bone remodeling(Chandra & Rajawat, 2021; Yousefzadeh et al., 2021; Zhang et al., 2022).

Importantly, hormonal changes (e.g., estrogen deficiency) and cellular senescence are independent but often converging drivers of skeletal aging (Farr et al., 2019; Manolagas, 2010). While many instances of osteoporosis and bone loss are attributed to hormonal causes, intrinsic aging mechanisms, such as telomere shortening, impair osteoblast proliferation and differentiation, which occur in parallel, linking systemic aging processes to skeletal decline independently of hormone status (Farr et al., 2019; Khosla et al., 2012; Marie, 2014). This distinction is critical both for developing therapeutic strategies, such as senolytics or

senomorphics, that specifically target senescent cells or their secretory output to improve skeletal health, as well as understanding how bone aging aligns with life history theory predictions (e.g., trade-offs between reproduction and maintenance) (López-Otín et al., 2023; Madimenos, 2015a; Wrona et al., 2024; Zhang et al., 2022). Overlapping demographic and behavioral factors, such as reproductive costs, impact both hormone exposure (Nguyen et al., 1995; Rasgon et al., 2005) and TL (Lin et al., 2011), and it is unclear whether these factors moderate, interact with, or simply exacerbate the effects of each other on bone aging. Exploring these relationships will enhance our understanding of bone aging and diversity in modern populations, providing insight into human evolution.

6.1.2 Telomere Length as a Biomarker of Biological Aging

Telomere length (TL) serves as both a driver and a biomarker of biological aging. Telomeres are repetitive nucleotide sequences that cap the ends of chromosomes, shortening with age, mitotic cellular division, and oxidative stress. Critically short telomeres activate DDR pathways, initiating cellular senescence to prevent further replication (Aviv, 2008; Hamad, Walter, et al., 2016). Shorter TL has been associated with an increased risk of age-related diseases (e.g., cardiovascular disease, diabetes, dementia) and higher all-cause mortality, supporting the interpretation of TL as an integrative biomarker of biological aging rather than a trait fixed strictly by chronological time. Accordingly, individuals with shorter TL, after adjusting for age, have shorter life expectancies (Cawthon et al., 2003; Ehrlenbach et al., 2009; Wang et al., 2018) In their fundamental work on the topic, López-Otín and colleagues (2013) included TL attrition as one of their Hallmarks of Aging, cellular and molecular drivers of organismal aging, and age-related pathologies (López-Otín et al., 2013, 2023).

TL has been associated with environmental exposures over the lifespan and inherited factors (e.g., paternal age effects, genetic ancestry). Psychosocial stress and socioeconomic status, for example, have been linked to TL(Beatty Moody et al., 2019; Chae et al., 2020; Geronimus et al., 2015; Hamad, Tuljapurkar, et al., 2016). Using TL data from NHANES, Needham et al. (2013) found that adults with less educational attainment (a proxy for lower socioeconomic status) had significantly shorter TL than their college-educated counterparts, after controlling for age, suggesting that environmental and social stressors can affect telomere attrition. Epidemiologic patterns of TL by racialized group and ethnicity demonstrate that individuals with recent African ancestry consistently have *longer* telomeres, on average, than those without, despite regular and often greater exposures to environmental and psychosocial stressors in contexts like the U.S. (Beatty Moody et al., 2019; Brown et al., 2017; Hansen et al., 2016; Hunt et al., 2008; Needham et al., 2020), emphasizing that both genetic ancestry and early-life environmental factors hold strong influences on TL and telomere dynamics.

Importantly, TL is not simply a passive marker of aging, accruing marks over time and exposure, but it is also a proxy for current and future cellular functioning. Researchers often use TL as a proxy for cumulative inflammatory and innate immune activation over an individual's lifetime and a mark of current and future immunological functioning. Individuals who experience increased exposure to infectious diseases throughout their lives have shorter TL (Eisenberg et al., 2017; Zanet et al., 2014); further, individuals with shorter TL appear to be more susceptible to infections (Cohen et al., 2013). Increased exposure to challenges leads to shorter TL, and shorter TL leads to lessened resilience against these challenges.

6.1.3 Telomere Length and Bone Mineral Density: Linking Cellular Aging to Skeletal Health

The dual role of TL as a proxy for past and cumulative exposures, as well as a signal of current and future cellular functioning, could make it especially relevant for bone biology and BMD changes with age. Here, TL, particularly TL attrition, may be especially relevant in bone-forming osteoblasts and their progenitors, where limited replicative potential and accumulated damage could compromise cell differentiation and matrix deposition.

Research using animal models has provided some initial connections between telomere biology and BMD. Saeed et al. (2011) studied the phenotype of telomerase-knockout mice (telomerase is principally important for TL maintenance) and found two mechanisms for age-related bone loss connected to telomerase deficiency. First, bone marrow stromal cells demonstrated reduced osteoblast differentiation and mineralization potential due to impaired proliferation and differentiation of mesenchymal stem cells (MSCs). Second, a pro-inflammatory bone microenvironment enhanced osteoclast activity in these mice. The result was an imbalance that mimicked age-related osteoporosis: impaired bone deposition coupled with increased, ongoing bone resorption (Saeed et al., 2011).

Several observational studies have provided evidence linking TL and reduced BMD in humans (Kakridonis et al., 2023; Sun et al., 2024; Tao et al., 2019). In a population-based study of 2,150 women, shorter TL was independently associated with lower BMD at the spine and forearm and with increased risk of clinical osteoporosis, particularly in women over the age of 50, suggesting that leukocyte telomere length may serve as a biomarker of skeletal aging (Valdes et al., 2007). Together, these results support the broader association between and a plausible mechanistic pathway linking TL and BMD loss: telomere attrition promotes senescent

osteoblasts and, thus, dysfunctional bone deposition, tipping the remodeling equilibrium toward net BMD loss.

Inflammation and immune function represent another set of factors connecting telomere attrition and osteoporosis. Extreme and chronically elevated inflammation and immune responses increase mitotic proliferation of white blood cells and oxidative stress. These processes accelerate TL shortening and hasten the rate of functional decline in proliferation-dependent processes (Eisenberg et al., 2017; Epel et al., 2004; Oikawa & Kawanishi, 1999; Osler et al., 2016; Von Zglinicki, 2002; Wrona et al., 2024). In bones, pro-inflammatory cytokines can inhibit osteoblast activity and promote osteoclast activity (Ginaldi et al., 2005; Pignolo et al., 2008; Saeed et al., 2011). Chronic inflammation accelerates bone resorption and suppresses bone formation, as seen in inflammatory diseases that cause osteoporosis (Okamoto et al., 2017; Wrona et al., 2024); therefore, inflammation may be a key pathway affecting both cellular aging and skeletal degeneration. Further, if TL shortening influences bone maintenance, then a pro-inflammatory state could represent a dangerous double-hit for bone health and aging.

Despite this theoretical and empirical support for a link between TL and BMD, the existing literature remains inconsistent. Sanders et al. (2009) reported that TL was *not* associated with BMD, osteoporosis diagnosis, or fracture incidence over a 7-year follow-up period in a large sample of older men and women from the Health ABC cohort (Sanders et al., 2009). These findings may, however, be the result of the relatively high mean age in Sanders' study population (mean age~75 years). This study could be affected by survivorship bias; age-related telomere shortening might have already plateaued in very old age, or the range of telomere lengths could have been too narrow to detect an effect on BMD. It is also possible that telomere length plays a more critical role earlier in the aging process or interacts with other factors (e.g., menopause or

mid-life health behaviors) not included in Sanders' analysis. A recent review by Wong and colleagues (2020) highlighted that the relationship between TL and bone health remains ambiguous across studies, suggesting that if TL influences bone aging, the effect may be context-dependent or mediated through third factors (Wong et al., 2020).

A 2022 Mendelian randomization study found evidence that longer telomeres *causally* reduced osteoporosis risk (OR ~0.85 per standard deviation increase in LTL). Interestingly, that causal signal weakened after accounting for sex hormone-binding globulin (SHBG) levels, which were causally linked to osteoporosis risk (Sun et al., 2024). SHBG is the primary mechanism through which sex steroids (e.g., testosterone, estradiol) are circulated through the body, hinting that at least part of the TL–BMD relationship may be influenced by hormonal pathways. Overall, the literature suggests that TL likely correlates with BMD and skeletal aging to some degree, but disentangling direct effects from confounders (e.g., collinear associations with age, inflammation, hormones) remains challenging and highlights the need for acknowledging multiple directions of relationships: from TL to bone remodeling, from inflammation to TL and bone, and the relationships between hormones, TL, and bone, among others.

This chapter adds to this body of knowledge by examining TL–BMD associations in a large, nationally representative U.S. sample, with careful attention to the moderating roles of age, sex, and other demographic factors, as well as the understanding that bone health is influenced by both macro-level (e.g., life history and demographic exposures) and micro-level processes (e.g., cellular aging and DNA maintenance).

6.1.4 Life History Constraints: Reproduction, Telomere Dynamics, and Bone Loss

Life History Theory posits that because resources are limited, organisms must trade off allocating energy towards growth, maintenance, and reproduction, providing another valuable perspective on aging and bone health (Kuzawa, 2007; Nettle & Frankenhuis, 2019; Stearns, 1989). In humans, the cost of reproduction hypothesis suggests that high reproductive effort (e.g., multiple pregnancies, prolonged lactation, short inter-birth intervals) may compromise somatic maintenance, including that of the skeletal system. Reproduction and obligatory care of altricial offspring diverts resources (e.g., nutrients) away from the maternal body, potentially leading to earlier or accelerated age-related decline(Baird et al., 2006; Jasienska, 2020b).

During pregnancy, the maternal body must supply calcium and other minerals to the developing fetal skeleton; during breastfeeding, calcium is actively mobilized from the maternal skeleton to enrich breast milk(Butte & King, 2005; Dufour & Sauther, 2002b; Jarlenski et al., 2014; Kalkwarf & Specker, 2002; Prentice & Prentice, 1988). Lactation-related losses can equal between 3-10% of total maternal bone mass, particularly from trabecular-rich regions, though much of this is typically recovered after weaning with adequate nutrition (Kalkwarf & Specker, 1995; Møller et al., 2012; Sohlström & Forsum, 1995). With repeated cycles of pregnancy and lactation or with pregnancies at advanced ages when bone recovery capacity is diminished, cumulative and excessive BMD loss could result (Lee, 2019). Some studies report that higher parity (number of childbirths) is associated with lower BMD or higher fracture risk in postmenopausal women, consistent with the cost of reproduction hypothesis. Allali et al. (2007) observed an inverse relationship between parity and BMD; each additional pregnancy was associated with decreased bone density (Allali et al., 2007). Similarly, a systematic review noted that very high parity (i.e., five or more children) was associated with an increased risk of

osteoporosis or fractures in populations experiencing greater energetic stress (Stieglitz et al., 2015a).

Other studies have found neutral (Lee, 2019) or positive (Murphy et al., 1994; Nguyen et al., 1995; Specker & Binkley, 2005) associations between childbearing and BMD, hypothesizing that the long-term endocrine changes of pregnancy (e.g., prolonged exposure to high estrogen levels) or post-pregnancy increases in body mass may offset any potential BMD losses. These mixed findings suggest that the impact of reproduction on maternal bone health may be contextually dependent on factors such as diet, lifestyle, birth spacing, and baseline health. Moderate levels of reproductive effort might be manageable; however, high-repetition reproductive efforts during nutritional scarcity may exact a more obvious toll on bone maintenance.

Reproduction has also been associated with molecular aging and TL in particular. Pregnancy, breastfeeding, and child-rearing are psychologically and physiologically demanding, involving vast changes in blood volume, inflammatory and immunological activation, hormonal fluctuations, sleep disruption, and often increased oxidative stress, all of which impact telomere maintenance. An analysis of U.S. women found that parous women had significantly shorter leukocyte telomeres than nulliparous women of the same age who had never had children (Pollack et al., 2018). The difference in TL equated to roughly 11 years of accelerated cellular aging in the parous women after adjusting for age and other factors. Ryan and colleagues also demonstrated that an increased number of children was associated with shorter TL among a cohort of Filipino women (C. P. Ryan et al., 2018). It is worth noting, however, that these cross-sectional studies do not establish causation; women who have children may differ in baseline telomere length or aging rate from those who do not, and factors such as stress or lack of social

support could mediate the observed differences (Houminer-Klepar et al., 2023). This said, studies with other species exhibit similar patterns; for example, birds with experimentally enlarged broods show faster telomere attrition (Sudyka et al., 2019).

6.1.5 Demographic Variation in Telomere Length and Bone Density

A central theme of this dissertation is how demographic factors, particularly sex and racialized group identity (White et al., 2011), influence patterns of physiological aging, as evident in bone density and telomere biology. Telomere length and BMD have been found to vary significantly across these groups (Araujo et al., 2007; Brown et al., 2017; George et al., 2003; Hansen et al., 2016; Hunt et al., 2008; Nam et al., 2013; Needham et al., 2013); see Chapter 5 for BMD differences), indicating a complex influence of hormonal, cellular, biomechanical, and genetic processes. The similarities and differences in these patterns, however, offer intriguing targets to disentangle the potential linkages and associations between these biological systems.

Sex differences in skeletal aging are pronounced. Males generally accrue greater peak bone mass early in adulthood, aided by higher testosterone levels and increased mechanical loading due to their typically larger body sizes. Females, conversely, begin with lower relative bone mass and experience a marked acceleration of BMD loss at menopause due to declining estrogen levels and face significantly higher risks of osteoporosis and fracture than men (Chandra & Rajawat, 2021; Dunsworth, 2020; Fischer & Mitteroecker, 2017; Raisz, 2005a; Shen et al., 2022; White et al., 2011).

Sex differences are generally apparent in TL as well, but TL tends to be longer in women than in age-matched men (Barrett & Richardson, 2011; Benetos et al., 2001; Brown et al., 2017;

Gardner et al., 2014), aligning with women's greater average lifespan and health span across populations. Estrogen likely contributes to this protective effect, as it promotes telomerase activity and reduces oxidative stress, potentially slowing telomere attrition in premenopausal women(Lin et al., 2011). Notably, women exhibit biologically younger cellular profiles (i.e., longer TL) but accelerated skeletal aging post-menopause, whereas men demonstrate faster telomeric aging (Barrett & Richardson, 2011) but more gradual skeletal decline. An open question explored here is whether the association between telomere length and BMD is sex- and age-specific. That is, are the associations potentially stronger in postmenopausal women or masked by slower turnover rates in men – both interactions which could further contribute to the heterogeneity in TL-BMD associations in previous studies.

The disparities in BMD with age between racialized groups are mirrored in TL. In the United States, Black adults typically possess higher BMD and lower fracture risk than White adults (Cauley et al., 2005), attributed partly to greater peak bone mass, differences in body composition, and physiological variations such as enhanced renal calcium retention among African ancestry groups. Conversely, White and Asian populations exhibit higher osteoporosis prevalence, with Asian women particularly vulnerable due to lower average body weight, a known risk factor for reduced BMD, and increased fracture incidence (Nam et al., 2013). Hispanic groups in the U.S., particularly Mexican Americans, generally present intermediate or slightly higher BMD compared to Whites, potentially reflecting genetic admixture, dietary differences, or heavier average body builds (Weaver et al., 2016).

Notably, these racialized patterns in bone health align with TL trends. Non-Hispanic Black Americans consistently show longer leukocyte telomeres than non-Hispanic Whites (Drury et al., 2015; Hamad, Tuljapurkar, et al., 2016; Hansen et al., 2016; Hunt et al., 2008; Walton et

al., 2016), and some evidence suggests that Hispanics also have relatively longer telomeres than Whites (Brown et al., 2017). The persistent TL advantage among Black Americans has sparked a debate: whether this difference represents genuine biological variation or methodological limitations (both in measurement and statistical methods) remains unresolved. If genuine, it raises the intriguing possibility that groups experiencing slower skeletal aging also exhibit slower cellular aging, suggesting overlapping biological mechanisms or developmental influences that confer both greater skeletal resilience and enhanced telomere maintenance.

This paper leverages data from NHANES – a demographically diverse and representative U.S. sample to investigate how these racialized patterns are recreated in the same individuals (as opposed to across studies and samples) and whether the telomere-BMD relationship holds consistently across groups or is modulated by demographic variables. Such analyses underscore that, overall, health and aging are deeply biosocial processes; relationships between cellular aging markers, such as TL, and skeletal health outcomes must be contextualized within the intersectional influences of sex, race/ethnicity, and life history. Ultimately, if TL emerges as a meaningful biomarker of bone aging, understanding its demographic variability will be critical for disentangling how they are related – do TL impact bone aging, do they share a third causal factor, or are they not associated?

6.2 AIMS

In this chapter, we integrate these lines of inquiry by examining relationships between LTL and BMD in a large, population-based sample of U.S. adults. We seek to determine whether LTL is associated with BMD and whether LTL may confound, moderate, or mediate the associations between demographic factors and BMD variations. We further investigate the role

of reproductive effort (proxied by parity) in female skeletal aging, specifically, whether women who have borne more children show evidence of shorter telomeres and whether LTL impacts the association between parity and BMD. We aim to elucidate a potential cellular mechanism (telomere dynamics) underlying population pattern in bone aging by addressing these questions.

6.2.1 Hypothesis 1.

Individuals with shorter telomeres will tend to have lower BMD, suggesting a relationship between cellular aging and skeletal integrity. We hypothesize a positive correlation between LTL and BMD, with shorter LTL associated with reduced BMD (after accounting for age, sex, and other covariates). Such a relationship could help explain why LTL and BMD demonstrate similar associations with life history variables such as reproduction and demographic variables such as racialized grouping.

6.2.2 Hypothesis 2.

Among women, greater parity (number of live births) will be associated with shorter LTL, indicating that cumulative reproductive exposure influences cellular aging rates.

6.2.3 Hypothesis 3.

Greater parity was associated with lower total BMD and the BMD of multiple measured regions in Chapter 4 (NHANES cohorts 2007-2018). We hypothesize that these relationships will exist in these cohorts and, further, that LTL will partially mediate this relationship – i.e., the bone density cost of multiple pregnancies may operate in part via accelerated telomere attrition. That is, higher investment in reproduction would lead to accelerated cellular aging (shorter LTL), impairing bone remodeling over the lifespan.

6.3 METHODS

6.3.1 Study Design and Population

These analyses utilize publicly available data from the U.S. National Health and Nutrition Examination Survey (NHANES), an ongoing series of cross-sectional, nationally representative health surveys conducted by the National Center for Health Statistics. NHANES uses a complex, multistage probability sampling design to assess the health and nutritional status of the civilian, non-institutionalized population. Within each two-year cohort, approximately 10,000 individuals are examined, with oversampling of certain groups (such as racial/ethnic minorities, low-income individuals, and older adults) adjusted at each sampling cycle to ensure adequate representation. Participants undergo extensive in-home interviews and physical examinations in mobile examination centers (MECs), where clinical measurements (e.g., DXA scans) and samples for laboratory tests are collected.

These analyses are focused on NHANES cycles spanning 1999-2002, during which both bone density and relevant covariate data were collected. Blood LTL was measured in a subset of participants in the 1999–2002 cycles (as described below), and dual-energy X-ray absorptiometry (DXA) scans of BMD were conducted. All participants provided written informed consent, and the NCHS Ethics Review Board approved the study protocols. The analytic use of de-identified public NHANES data was deemed exempt from additional IRB review.

6.3.2 Bone Mineral Density Measurement

BMD was measured by DXA as part of the NHANES physical examination. During each survey cycle, whole-body DXA scans were administered by certified radiologic technologists

following standardized protocols overseen by a centralized quality control center. Between 1999 and 2002, a Hologic QDR 4500A fan-beam densitometer was used for whole-body scans. All machines were calibrated daily with anthropomorphic phantoms, and rigorous quality control procedures ensured consistency of BMD measurements across time and equipment changes.

Participants lay supine on the DXA table for the scan, and a low-dose X-ray beam at two energy levels was passed over the body to quantify bone mineral content; the radiation dose per scan was extremely low (on the order of 4–8 μSv, less than 1% of annual background radiation). Exclusion criteria for the DXA exam included pregnancy and excessive body size. All adult women underwent a urine pregnancy test on-site; those who tested positive were excluded from DXA to avoid fetal radiation exposure. Likewise, individuals whose body weight exceeded ~136 kg (300 lbs.) or height exceeded 197 cm (6'5") could not be scanned due to device limitations.

NHANES performed whole-body scans (yielding total body BMD and regional BMD estimates for the arms, legs, trunk, etc.) and specialized femur scans to obtain proximal femur (hip) BMD at the femoral neck and total hip. In some later cycles, dedicated lumbar spine DXA scans were also performed on older adults (see previous chapters); however, site-specific spine measures were unavailable in the 1999–2002 cycles used for telomere analysis. All BMD data were processed using manufacturer-provided calibration adjustments to account for machine differences over time and were reviewed by the NHANES DXA quality control center to ensure accuracy. BMD values were standardized by population and gender-specific subpopulation where relevant to aid interpretation and used as outcome variables in the regressions for Hypotheses 1 and 3 (*see 6.3.8. Regression Models*).

6.3.3 Telomere Length Measurement

LTL was measured in a subset of NHANES participants aged 20 and older using banked DNA samples extracted from whole blood. DNA was extracted from whole blood using standardized procedures and stored at −80°C. Samples were assayed by the laboratory of Dr. Elizabeth Blackburn at the University of California, San Francisco, using the quantitative polymerase chain reaction (PCR) method to generate average LTL relative to standard reference DNA (mean T/S ratio), as described in detail elsewhere (Cawthon, 2002; Lin et al., 2010). Human beta-globin was used as the housekeeping gene of known copy number.

Each sample was tested in duplicate on three different plates (run on separate days), producing six measurements per individual. Eight control samples were included on each 96-well plate, and runs were rejected if control wells fell outside predefined limits (i.e., >4 control wells that are >2.5 SD from the overall control mean). Less than 1% of runs and 2% of samples failed quality control criteria. The inter-assay coefficient of variation for the telomere length assay was 6.5%. After applying quality control filters, LTL data were merged with BMD data for adults with complete covariates. Our final sample with both LTL and BMD data consisted of n = 3,565 adults. This telomere subsample included 1,939 men and 1,626 women, aged 20-79 (mean approximately 43.85 years).

6.3.4 Demographic Variables

To test whether demographic differences in LTL parallel those found in BMD, we included age, gender, and self-reported racialized group as collected via NHANES household interviews. The participant's age in years was reported at the time of examination. Gender was recorded as male or female (see "On Sex and Gender" above). Racialized grouping categories

are derived from the NHANES survey data collection protocol for the "RIDRETH1" variable. Participant racialized grouping was determined by self-identification into one of five categories: "Mexican American," "Other Hispanic," "Non-Hispanic White," Non-Hispanic Black," and "Other, including multi-racial" identities. Respondents who self-identified as "Mexican American" were coded as such in NHANES, regardless of their other race-ethnicity identities. Otherwise, self-identification as "Hispanic" results in categorization as "Other Hispanic." All other non-Hispanic participants were then categorized based on their self-reported racialized grouping, as noted above.

6.3.5 Reproductive History

Parity, for this chapter, refers to a participant's total number of live births, as collected from the NHANES Reproductive Health Questionnaire (RHQ). The calculation of parity here differs slightly from Chapter 3, as data on the total number of deliveries were unavailable for the 1999-2002 cohorts. Participants with parity values above 11 were coded in NHANES as 11. Other reproductive variables, such as the frequency or duration of breastfeeding, were not uniformly available for all cycles and were therefore not included in the primary analyses (although we address their potential impact in the Discussion).

6.3.6 Control Variables

Additional variables could influence LTL and BMD but lie outside of our hypothesized pathways of interest, i.e., LTL influencing BMD. Collected via NHANES questionnaires, control variables include body mass index (BMI), educational attainment, family poverty income ratio (FPIR), smoking behavior, and alcohol use (see previous chapters for details).

6.3.7 Statistical Analysis

We used a series of multiple linear regression models to test whether 1) LTL is associated with BMD, 2) parity is associated with LTL and 3) LTL influences the association between parity and BMD (whether through confounding, moderation, or mediation). The general sets of regressions across each hypothesis mirrors those conducted for Chapter 4. Regression models are explicitly defined below in section *6.3.8*.

For Hypotheses 1 and 2, we conducted three linear regressions ranging from a minimally to maximally adjusted model. For Hypothesis 3, we conducted two sets of three linear regressions ranging from a minimally to maximally controlled model: one set included LTL, and one set did not include LTL. Minimally controlled models included only the predictor of interest and the outcome of interest (e.g., H1a contains only BMD and LTL adjusted for age). The second model for each hypothesis additionally included age and BMI. The maximally controlled model for each hypothesis included age and BMI along with the rest of our control variables: self-identified racialized groups, educational level, FPIR, smoking behavior, and alcohol use. For Hypothesis 1, these models were then stratified by gender (testing women and men separately) to explore whether genders differed in LTL and BMD associations. Gender-related variables were removed in these gender-restricted analyses. Hypotheses 2 and 3 were only conducted in women and the maximally controlled models additionally included age at menarche (years) and lifetime estrogen exposure total number of years between menarche and the most recent menstrual cycle, combined with the lifetime duration of HRT use, calculated as the total time, in years, a participant recalls having used estrogen-only, or estrogen-progesterone combination pills or patches. If the coefficients of the key independent variables (e.g., LTL in H1) are substantially

reduced as additional covariates are added, this is interpreted as evidence that these covariates are at least partially confounding, moderating, or mediating the association of interest.

Mean T/S ratios were z-transformed before all analyses (Verhulst, 2020). When both genders are included, mean T/S ratios are z-transformed over the entire sample. When a single gender is included (e.g., H2), then mean T/S ratios are z-transformed over participants in that gender only. To adjust for collinearity between LTL and age in models where LTL is a predictor variable (i.e., H1 and H3), we calculated sample-specific age-adjusted LTL using these z-transformed scores. This was done by regressing LTL on age within each analytic sample and using the standardized residuals from that regression in their respective models. For example, in H3, age-adjusted LTL scores by regressing LTL on age in women only. These age-adjusted LTL residuals capture variation in LTL independent of age, allowing for a clearer interpretation of LTL–BMD associations. All analyses are performed in Stata 18 SE.

6.3.8 Regression Models

H1

- H1a. BMD ~ LTL (age-adjusted) + gender

  By gender: BMD ~ LTL (age-adjusted)
- H1b. BMD ~ LTL (age-adjusted) + gender + age + BMI

  By gender: BMD ~ LTL (age-adjusted) + age + BMI
- H1c. BMD ~ LTL (age-adjusted) + gender + age + BMI + Educational Attainment + Family Poverty Income Ratio + Smoking Status + Alcohol Use

By gender: BMD ~ LTL (age-adjusted) + age + BMI + Educational Attainment + Family Poverty Income Ratio + Smoking Status + Alcohol Use

H2

- H2a. LTL ~ parity
- H2b. LTL ~ parity + age
- H2c. LTL ~ parity + age + lifetime estrogen exposure + age at menarche + Educational Attainment + Family Poverty Income Ratio + Smoking Status + Alcohol Use

H3

- H3a.
  - H3a.1. BMD ~ parity
  - H3a.2. BMD ~ parity + age + BMI
  - H3a.3. BMD ~ parity + age + BMI + lifetime estrogen exposure + age at menarche + Educational Attainment + Family Poverty Income Ratio + Smoking Status + Alcohol Use
- H3b.
  - H3b.1. BMD ~ parity + LTL(age-adjusted)
  - H3b.2. BMD ~ parity + LTL(age-adjusted) + age + BMI
  - H3b.3. BMD ~ parity + LTL(age-adjusted) + age + BMI + lifetime estrogen exposure + age at menarche + Educational Attainment + Family Poverty Income Ratio + Smoking Status + Alcohol Use

6.4 RESULTS

6.4.1 Descriptive statistics

After applying our exclusion criteria, the final analytical sample included 3,565 adults aged 20-79 (mean age: 43.86 years). Detailed regression results are provided in the Supplementary Information.

6.4.2 Hypothesis 1. Telomere Length and Bone Mineral Density

In our full sample, mean LTL was positively associated with Total BMD ($\beta = 0.036$, $p < 0.01$) and average leg BMD ($\beta = 0.035$, $p < 0.01$) in the model controlling for gender, age, and BMI. That is, longer LTL was associated with higher BMD in these regions. In our maximally controlled models, however, these associations were attenuated and no longer significant. In our men-only analyses, we did not find any significant associations between mean LTL and full or regional BMD at the $p<0.01$ level. We did, however, find multiple positive associations between mean LTL and BMD in our women-only analysis. First, there was a positive association between mean LTL and average arm BMD in the model controlling for age and BMI ($\beta = 0.058$, $p < 0.01$), which was somewhat attenuated and lost significance in the maximally controlled model ($\beta = 0.049$, $p < 0.05$). Second, there is a positive association between mean LTL and average leg BMD when controlling for age and BMI ($\beta = 0.052$, $p < 0.01$). This association is lost in the maximally controlled model ($\beta = 0.029$, $p > 0.10$).

Importantly, the associations between demographic variables and BMD from Chapters 4 and 5 were reproduced, despite the inclusion of LTL, the necessary omission of sedentary time as a covariate, and the lack of overlap between sample participants (previous chapters drew data from the 2007-2018 cohorts). Age was negatively associated with BMD, and men had higher

total BMD with a slower age-related decline across total BMD and all regional BMDs. Further, non-Hispanic Black participants had higher BMD, whereas Mexican American, Other Hispanic, and multiracial participants generally had lower BMD compared to non-Hispanic Whites. These patterns were largely consistent across total and regional BMD (See Tables 5-7).

Table 5. Chapter 6 - Hypothesis 1 Results - Total Sample

Variable	Total BMD			Lumbar BMD			Thoracic Spine BMD			Avg Arm BMD			Avg Leg BMD			Avg Rib BMD			Pelvis BMD		
TL (age-adjusted)	0.029**	**0.036***	0.003	0.024	0.027*	0.002	0.020	0.034**	0.020	0.017*	0.022**	0.002	0.026**	**0.035***	0.001	0.007	0.016	-0.021	0.01	0.029**	-0.001
	(0.013)	**(0.012)**	(0.014)	(0.015)	(0.015)	(0.017)	(0.014)	(0.014)	(0.016)	(0.010)	(0.010)	(0.011)	(0.012)	**(0.011)**	(0.013)	(0.013)	(0.013)	(0.015)	(0.015)	(0.013)	(0.015)
Gender	**0.577*** **	**0.589*** **	**0.567*** **	0.062**	0.069**	0.014	**0.378*** **	**0.399*** **	**0.343*** **	**1.195*** **	**1.205*** **	**1.182*** **	**0.963*** **	**0.979*** **	**0.954*** **	**0.790*** **	**0.806*** **	**0.810*** **	**0.341*** **	**0.373*** **	**0.311*** **
	(0.023)	**(0.022)**	**(0.026)**	(0.028)	(0.027)	(0.033)	(0.026)	(0.025)	(0.031)	(0.018)	(0.018)	(0.021)	(0.022)	**(0.020)**	(0.024)	(0.024)	(0.023)	(0.028)	(0.027)	(0.024)	(0.029)
Age		**-0.013*** **	**-0.012*** **	**-0.008*** **	**-0.007*** **		-0.001	0.000		**-0.010*** **	**-0.009*** **			**-0.013*** **	**-0.012*** **		**-0.015*** **	**-0.015*** **		**-0.018*** **	**-0.017*** **
		(0.001)	**(0.001)**	**(0.001)**	**(0.001)**		(0.001)	(0.001)		**(0.001)**	**(0.001)**			**(0.001)**	**(0.001)**		**(0.001)**	**(0.001)**		**(0.001)**	**(0.001)**
BMI		**0.021*** **	**0.024*** **	**0.011*** **	**0.013*** **		**0.045*** **	**0.048*** **		**0.016*** **	**0.018*** **			**0.029*** **	**0.035*** **		**0.027*** **	**0.027*** **		**0.060*** **	**0.064*** **
		(0.002)	**(0.003)**	**(0.003)**	**(0.004)**		**(0.003)**	**(0.003)**		**(0.002)**	**(0.002)**			**(0.002)**	**(0.003)**		**(0.003)**	**(0.003)**		**(0.003)**	**(0.003)**
Family Poverty Income Ratio			**0.025*** **		0.004			**0.031*** **			**0.023*** **				**0.024*** **			0.008			**0.028*** **
			(0.009)		(0.012)			**(0.011)**			(0.008)				(0.009)			(0.010)			**(0.010)**
# Weekly Drinks			0.002		0.001			0.000			0.003**				0.003*			0.001			0.003*
			(0.002)		(0.002)			(0.002)			(0.001)				(0.002)			(0.002)			(0.002)
Racialized Group (Reference group is white)																					
Black			**0.318*** **		**0.388*** **			**0.294*** **			**0.195*** **				**0.208*** **			**0.404*** **			**0.329*** **
			(0.038)		**(0.048)**			**(0.045)**			**(0.031)**				**(0.035)**			**(0.041)**			**(0.042)**
Mexican			**-0.271*** **		**-0.268*** **			**-0.109*** **			**-0.245*** **				**-0.272*** **			**-0.179*** **			**-0.217*** **
			(0.037)		**(0.046)**			**(0.042)**			**(0.029)**				**(0.034)**			(0.039)			**(0.040)**
Other Hispanic			**-0.167*** **		-0.163**			-0.101			**-0.200*** **				**-0.212*** **			0.012			-0.161**
			(0.058)		(0.073)			(0.067)			**(0.046)**				**(0.053)**			(0.062)			(0.063)
Other (incl. multiracial)			-0.163*		-0.053			0.109			**-0.288*** **				-0.178**			-0.217**			-0.124
			(0.083)		(0.105)			(0.096)			**(0.067)**				(0.076)			(0.089)			(0.091)
Education (Reference group is <9th grade)																					
9-11th grade (incl. 12th w/ no diploma)			0.094*		0.115*			0.037			0.102**				0.116**			0.062			0.128**
			(0.051)		(0.064)			(0.059)			(0.041)				(0.047)			(0.054)			(0.055)
High School Grad/GED or equivalent			0.099*		0.102			0.006			0.035				0.114**			0.083			0.098*
			(0.051)		(0.064)			(0.059)			(0.041)				(0.047)			(0.055)			(0.056)
Some college or AA degree			**0.150*** **		**0.165*** **			0.029			0.038				**0.208*** **			0.065			**0.148*** **
			(0.052)		(0.065)			(0.060)			(0.042)				**(0.046)**			(0.055)			**(0.056)**
College graduate or above			0.138**		0.180**			0.014			-0.043				**0.201*** **			-0.007			0.077
			(0.056)		(0.071)			(0.065)			(0.045)				**(0.052)**			(0.060)			(0.061)
Smoking Status (Reference group is non-smokers)																					
Former smokers			-0.058		-0.011			0.045			-0.013				-0.054			-0.044			-0.069*
			(0.038)		(0.048)			(0.044)			(0.030)				(0.035)			(0.040)			(0.041)
Current Smokers			-0.075*		-0.054			-0.024			-0.048				-0.038			-0.063			-0.109**
			(0.041)		(0.052)			(0.048)			(0.033)				(0.038)			(0.044)			(0.045)
Heavy Smokers			-0.056		-0.002			-0.004			0.014				-0.070**			-0.061			-0.064
			(0.037)		(0.047)			(0.043)			(0.030)				(0.034)			(0.039)			(0.040)
Observations	3,565	3,565	2,484	3,565	2,484	3,565	3,565	2,484	3,565	3,565	2,484	3,565	3,565	3,565	2,484	3,565	3,565	2,484	3,565	3,565	2,484
R-squared	0.146	0.222	0.283	0.002	0.024	0.093	0.056	0.119	0.150	0.542	0.584	0.611	0.355	0.432	0.478	0.227	0.315	0.360	0.044	0.242	0.284

Standard errors in parentheses

*** p<0.01, ** p<0.05, * p<0.1

Table 6. Chapter 6 - Hypothesis 1 Results – Women Only Subsample

Variable	Total BMD			Lumbar BMD			Thoracic Spine BMD			Avg Arm BMD			Avg Leg BMD			Avg Rib BMD			Pelvis BMD		
TL (age-adjusted)	0.033	0.050**	0.040*	0.022	0.034	0.032	0.023	0.046**	0.065**	0.041**	**0.058*** **	0.049**	0.028	**0.052*** **	0.029	-0.010	0.017	-0.024	0.006	0.039*	0.028
	(0.021)	(0.020)	(0.023)	(0.023)	(0.022)	(0.027)	(0.022)	(0.021)	(0.026)	(0.020)	**(0.018)**	(0.021)	(0.021)	**(0.019)**	(0.022)	(0.022)	(0.020)	(0.024)	(0.023)	(0.021)	(0.025)
Age		**-0.019*** **	**-0.019*** **		**-0.017*** **	**-0.016*** **		**-0.012*** **	**-0.011*** **		**-0.021*** **	**-0.020*** **		**-0.020*** **	**-0.020*** **		**-0.021*** **	**-0.021*** **		**-0.021*** **	**-0.020*** **
		(0.001)	**(0.002)**		**(0.001)**	**(0.002)**		**(0.001)**	**(0.002)**		**(0.001)**	**(0.001)**		**(0.001)**	**(0.001)**		**(0.001)**	**(0.002)**		**(0.001)**	**(0.002)**
BMI		**0.017*** **	**0.018*** **		**0.008***	**0.004**		**0.039*** **	**0.041*** **		**0.014*** **	**0.014*** **		**0.031*** **	**0.036*** **		**0.036*** **	**0.033*** **		**0.050*** **	**0.052*** **
		(0.004)	**(0.004)**		**(0.004)**	**(0.005)**		**(0.004)**	**(0.005)**		**(0.003)**	**(0.004)**		**(0.003)**	**(0.004)**		**(0.004)**	**(0.005)**		**(0.004)**	**(0.005)**
Family Poverty Income Ratio			0.021			0.019			0.054***			0.017			0.019			-0.001			0.015
			(0.016)			(0.018)			(0.018)			(0.015)			(0.015)			(0.016)			(0.017)
# Weekly Drinks			0.001			0.005			0.006			0.009*			0.008			-0.003			0.009
			(0.005)			(0.006)			(0.006)			(0.005)			(0.005)			(0.006)			(0.006)
Racialized Group (Reference group is white)																					
Black			**0.275*** **			**0.309*** **			**0.164** **			**0.316*** **			**0.167*** **			**0.440*** **			**0.338*** **
			(0.065)			**(0.075)**			**(0.072)**			**(0.060)**			**(0.061)**			**(0.067)**			**(0.070)**
Mexican			**-0.200*** **			-0.179**			-0.077			**-0.246*** **			**-0.265*** **			-0.161**			-0.162**
			(0.062)			(0.071)			(0.069)			**(0.057)**			**(0.058)**			(0.064)			(0.067)
Other Hispanic			-0.185*			-0.131			-0.171			**-0.284*** **			**-0.274*** **			-0.008			-0.205*
			(0.098)			(0.114)			(0.110)			**(0.090)**			**(0.092)**			(0.101)			(0.107)
Other (incl. multiracial)			0.065			-0.071			0.258*			-0.192			0.006			-0.051			-0.010
			(0.139)			(0.161)			(0.155)			(0.128)			(0.131)			(0.143)			(0.151)
Education (Reference group is <9th grade)																					
9-11th grade (incl. 12th w/ no diploma)			0.095			**0.310*** **			0.148			0.121			0.082			0.035			0.121
			(0.099)			**(0.115)**			(0.111)			(0.092)			(0.094)			(0.103)			(0.108)
High School Grad/GED or equivalent			0.182*			**0.317*** **			0.067			0.082			0.174*			0.061			0.128
			(0.097)			**(0.112)**			(0.108)			(0.089)			(0.091)			(0.100)			(0.105)
Some college or AA degree			0.165*			**0.391*** **			0.130			0.021			0.182**			0.022			0.136
			(0.096)			**(0.111)**			(0.107)			(0.088)			(0.090)			(0.099)			(0.104)
College graduate or above			0.266**			**0.429*** **			0.178			0.094			**0.315*** **			0.068			0.144
			(0.104)			**(0.120)**			(0.116)			(0.096)			**(0.098)**			(0.107)			(0.113)
Smoking Status (Reference group is non-smokers)																					
Former smokers			-0.078			0.002			0.004			-0.049			-0.053			0.014			-0.082
			(0.068)			(0.079)			(0.076)			(0.063)			(0.064)			(0.070)			(0.074)
Current Smokers			-0.087			-0.073			-0.001			-0.042			-0.041			-0.081			-0.084
			(0.075)			(0.087)			(0.084)			(0.069)			(0.071)			(0.077)			(0.082)
Heavy Smokers			-0.046			0.025			-0.007			0.036			-0.046			-0.057			0.031
			(0.065)			(0.076)			(0.073)			(0.060)			(0.062)			(0.067)			(0.071)
Observations	1,626	1,626	1,006	1,626	1,626	1,006	1,626	1,626	1,006	1,626	1,626	1,006	1,626	1,626	1,006	1,626	1,626	1,006	1,626	1,626	1,006
R-squared	0.001	0.159	0.210	0.001	0.096	0.156	0.001	0.095	0.123	0.003	0.205	0.260	0.001	0.196	0.267	0.000	0.197	0.246	0.000	0.216	0.251

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Table 7. Chapter 6 - Hypothesis 1 Results – Men Only Subsample

Variable	Total BMD			Lumbar BMD			Thoracic Spine BMD			Avg Arm BMD			Avg Leg BMD			Avg Rib BMD			Pelvis BMD		
TL (age-adjusted)	0.033	0.050**	0.040*	0.022	0.034	0.032	0.023	0.046**	0.055**	0.041**	0.058***	0.049**	0.028	0.052***	0.029	-0.010	0.017	-0.024	0.006	0.039*	0.028
	(0.021)	(0.020)	(0.023)	(0.023)	(0.022)	(0.027)	(0.022)	(0.021)	(0.026)	(0.020)	(0.018)	(0.021)	(0.021)	(0.019)	(0.022)	(0.022)	(0.020)	(0.024)	(0.023)	(0.021)	(0.025)
Age		-0.019***	-0.019***		-0.017***	-0.016***		-0.012***	-0.011***		-0.021***	-0.020***		-0.020***	-0.020***		-0.021***	-0.021***		-0.021***	-0.020***
		(0.001)	(0.002)		(0.001)	(0.002)		(0.001)	(0.002)		(0.001)	(0.001)		(0.001)	(0.001)		(0.001)	(0.002)		(0.001)	(0.002)
BMI		0.017***	0.016***		0.008*	0.004		0.039***	0.041***		0.014***	0.014***		0.031***	0.036***		0.036***	0.033***		0.050***	0.052***
		(0.004)	(0.004)		(0.004)	(0.005)		(0.004)	(0.005)		(0.003)	(0.004)		(0.003)	(0.004)		(0.004)	(0.005)		(0.004)	(0.005)
Family Poverty Income Ratio			0.021			0.019			0.054***			0.017			0.019			-0.001			0.015
			(0.016)			(0.018)			(0.018)			(0.015)			(0.015)			(0.016)			(0.017)
# Weekly Drinks			0.001			0.005			0.006			0.009*			0.008			-0.003			0.009
			(0.005)			(0.006)			(0.006)			(0.005)			(0.005)			(0.006)			(0.006)
Racialized Group (Reference group is white)																					
Black			0.275***			0.309***			0.164**			0.316***			0.167***			0.440***			0.338***
			(0.065)			(0.075)			(0.072)			(0.060)			(0.061)			(0.067)			(0.070)
Mexican			-0.200***			-0.179**			-0.027			-0.246***			-0.265***			-0.161**			-0.162**
			(0.062)			(0.071)			(0.069)			(0.057)			(0.058)			(0.064)			(0.067)
Other Hispanic			-0.185*			-0.131			-0.171			-0.284***			-0.274***			-0.008			-0.205*
			(0.098)			(0.114)			(0.110)			(0.090)			(0.092)			(0.101)			(0.107)
Other (incl. multiracial)			0.065			-0.071			0.258*			-0.192			0.006			-0.051			-0.010
			(0.139)			(0.161)			(0.155)			(0.128)			(0.131)			(0.143)			(0.151)
Education (Reference group is <9th grade)																					
9-11th grade (incl. 12th w/ no diploma)			0.095			0.310***			0.148			0.121			0.082			0.035			0.121
			(0.099)			(0.115)			(0.111)			(0.092)			(0.094)			(0.103)			(0.108)
High School Grad/GED or equivalent			0.182*			0.317***			0.067			0.082			0.174*			0.061			0.128
			(0.097)			(0.112)			(0.108)			(0.089)			(0.091)			(0.100)			(0.105)
Some college or AA degree			0.165*			0.391***			0.130			0.021			0.182**			0.022			0.136
			(0.096)			(0.111)			(0.107)			(0.088)			(0.090)			(0.099)			(0.104)
College graduate or above			0.266**			0.429***			0.178			0.094			0.315***			0.068			0.144
			(0.104)			(0.120)			(0.116)			(0.096)			(0.098)			(0.107)			(0.113)
Smoking Status (Reference group is non-smokers)																					
Former smokers			-0.078			0.002			0.004			-0.049			-0.053			0.014			-0.062
			(0.068)			(0.079)			(0.076)			(0.063)			(0.064)			(0.070)			(0.074)
Current Smokers			-0.087			-0.073			-0.001			-0.042			-0.041			-0.081			-0.084
			(0.075)			(0.087)			(0.084)			(0.069)			(0.071)			(0.077)			(0.082)
Heavy Smokers			-0.046			0.025			-0.007			0.036			-0.046			-0.057			0.031
			(0.095)			(0.079)			(0.073)			(0.060)			(0.062)			(0.067)			(0.071)
Observations	1,626	1,626	1,006	1,626	1,626	1,006	1,626	1,626	1,006	1,626	1,626	1,006	1,626	1,626	1,006	1,626	1,626	1,006	1,626	1,626	1,006
R-squared	0.001	0.159	0.210	0.001	0.096	0.156	0.001	0.095	0.123	0.003	0.205	0.260	0.001	0.195	0.267	0.000	0.197	0.246	0.000	0.216	0.251

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

6.4.3 Hypothesis 2. Reproductive History and Telomere Length

As we expected, parity was directly, negatively associated with mean LTL in our minimally controlled model ($\beta = -0.090$, $p < 0.01$), however, it was not associated with LTL in our second ($\beta = -0.019$, $p > 0.10$) or maximally controlled models ($\beta = 0.027$, $p > 0.10$). Conversely, our demographic variables demonstrated expected associations with LTL. Older age and higher BMI were each associated with shorter LTL ($\beta = -0.024$, $p < 0.01$ for both) and Blacks had longer LTL ($\beta = 0.029$, $p > 0.10$) and Mexican-Americans had shorter LTL ($\beta = 0.029$, $p > 0.10$). Notably, none of the reproductive history variables (i.e., lifetime estrogen exposure and age at menarche), FPIR, education level, number of weekly drinks, and smoking behavior were associated with mean LTL (all $p > 0.10$), contradicting our predictions (See Table 8).

Table 8. Chapter 6 - Hypothesis 2 Results

Variable		TL[a]	TL[b]	TL[c]
Parity		-0.090***	-0.019	0.027
		(0.012)	(0.013)	(0.024)
Age			-0.021***	-0.024***
			(0.002)	(0.004)
BMI				-0.024***
				(0.007)
Family Poverty Income Ratio				-0.025
				(0.025)
Lifetime Estrogen Exposure				0.000
				(0.005)
Age at menarche				-0.026
				(0.022)
# Weekly Drinks				-0.002
				(0.009)
Racialized Group (Reference group is white)				
	Black			0.298***
				(0.102)
	Mexican			-0.396***
				(0.101)
	Other Hispanic			-0.167
				(0.151)
	Other (incl. multiracial)			-0.283
				(0.211)
Education (Reference group is <9th grade)				
	9-11th grade (incl. 12th w/ no diploma)			-0.063
				(0.163)
	High School Grad/GED or equivalent			0.122
				(0.155)
	Some college or AA degree			0.056
				(0.156)
	College graduate or above			0.036
				(0.169)
Smoking Status (Reference group is non-smokers)				
	Former smokers			-0.060
				(0.111)
	Current Smokers			-0.066
				(0.126)
	Heavy Smokers			-0.201*
				(0.102)
Observations		1,549	1,549	748
R-squared		0.034	0.124	0.188

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

6.4.4 Hypothesis 3. Reproductive History, Telomere Length, and Bone Mineral Density

Lastly, to evaluate whether LTL influences the relationship between parity and BMD, we 1) tested whether parity is associated with BMD and 2) examined whether the association between parity and BMD changed when age-adjusted LTL was included in the model. First, we found multiple negative associations between parity and BMD in this cohort (i.e., higher parity is

associated with lower BMD). In the minimally adjusted model, there was a direct, negative association between parity and BMD in all tested regions (7 tested regions) at $p<0.01$. Adding age weakened many of these associations, such that only parity-BMD associations in the lumbar spine and the average leg BMD remained significant. Further, there were no significant associations in the maximally controlled models.

Next, we found associations between mean LTL and average arm BMD ($\beta = 0.044$, $p < 0.01$) and average leg BMD ($\beta = 0.041$, $p < 0.01$), replicating our results from H1. Further, the mean LTL-average arm BMD coefficient remained significant in the maximally controlled model. Importantly, the coefficients for parity's association with BMD did not change for any region or total BMD when LTL was added to the model, even when LTL had a significant effect. For example, looking at the results for average leg BMD where LTL had a large, significant association, the coefficient for parity remains the same regardless of whether LTL is included (i.e., $\beta = -0.040$) (See Tables 9 & 10).

Table 9. Chapter 6 - Hypothesis H3a Results

Variable	Total BMD			Lumbar BMD			Thoracic Spine BMD			Avg Arm BMD			Avg Leg BMD			Avg Rib BMD			Pelvis BMD		
Hypothesis	H3a1	H3a2	H3a3	H3a1	H3a2	H3a3	H3a1	H3a2	H3a3	H3a1	H3a2	H3a3	H3a1	H3a2	H3a3	H3a1	H3a2	H3a3	H3a1	H3a2	H3a3
Parity	**-0.071*** **	-0.021**	0.016	**-0.089*** **	**-0.046*** **	-0.011	**-0.041*** **	-0.024**	0.011	**-0.062*** **	**-0.017*** **	0.007	**-0.077*** **	**-0.040*** **	-0.007	**-0.066*** **	-0.021**	-0.002	**-0.061*** **	-0.016*	0.015
	(0.009)	(0.009)	(0.015)	**(0.010)**	**(0.011)**	(0.019)	**(0.009)**	(0.010)	(0.017)	**(0.006)**	**(0.007)**	(0.011)	**(0.007)**	**(0.008)**	(0.013)	**(0.008)**	(0.009)	(0.015)	**(0.009)**	(0.010)	(0.017)
Age		**-0.017*** **	**-0.031*** **		**-0.013*** **	**-0.028*** **		**-0.010*** **	**-0.023*** **		**-0.014*** **	**-0.023*** **		**-0.014*** **	**-0.023*** **		**-0.017*** **	**-0.023*** **		**-0.019*** **	**-0.039*** **
		(0.001)	**(0.003)**		**(0.001)**	**(0.003)**		**(0.001)**	**(0.003)**		**(0.001)**	**(0.002)**		**(0.001)**	**(0.002)**		**(0.001)**	**(0.003)**		**(0.001)**	**(0.003)**
BMI		**0.014*** **	**0.020*** **		0.008*	0.007		**0.034*** **	**0.041*** **		**0.009*** **	**0.010*** **		**0.025*** **	**0.033*** **		**0.030*** **	**0.030*** **		**0.044*** **	**0.051*** **
		(0.003)	**(0.005)**		(0.004)	(0.006)		**(0.004)**	**(0.005)**		**(0.002)**	**(0.003)**		**(0.003)**	**(0.004)**		**(0.003)**	**(0.005)**		**(0.004)**	**(0.005)**
Family Poverty Income Ratio			0.015			0.016			0.039**			0.015			0.016			-0.001			0.015
			(0.016)			(0.020)			(0.018)			(0.012)			(0.013)			(0.016)			(0.018)
# Weekly Drinks			0.008			0.007			0.009			**0.012*** **			**0.013*** **			0.001			0.012*
			(0.006)			(0.007)			(0.006)			**(0.004)**			**(0.005)**			(0.006)			(0.006)
Lifetime Estrogen Exposure			**0.016*** **			**0.016*** **			**0.013*** **			**0.011*** **			**0.009*** **			0.004			**0.013*** **
			(0.003)			**(0.004)**			**(0.004)**			**(0.002)**			**(0.003)**			(0.003)			**(0.003)**
Age at Menarche			0.016			-0.004			0.011			**0.030*** **			0.025**			0.015			0.015
			(0.014)			(0.017)			(0.016)			**(0.010)**			(0.012)			(0.014)			(0.016)
Racialized Group (Reference group is white)																					
Black			**0.256*** **			**0.327*** **			0.154**			**0.252*** **			0.108**			**0.344*** **			**0.303*** **
			(0.065)			**(0.080)**			(0.073)			**(0.047)**			(0.054)			**(0.063)**			**(0.072)**
Mexican			-0.161**			-0.164**			-0.001			**-0.165*** **			**-0.209*** **			-0.125**			-0.165**
			(0.065)			(0.080)			(0.073)			**(0.047)**			**(0.054)**			(0.062)			(0.071)
Other Hispanic			-0.129			-0.147			-0.176			-0.164**			-0.195**			-0.031			-0.136
			(0.097)			(0.119)			(0.109)			(0.070)			(0.080)			(0.093)			(0.106)
Other (incl. multiracial)			0.065			0.015			0.282*			-0.155			0.023			-0.012			0.022
			(0.136)			(0.167)			(0.152)			(0.098)			(0.112)			(0.131)			(0.149)
Education (Reference group is <9th grade)																					
9-11th grade (incl. 12th w/ no diploma)			0.112			0.302**			0.135			0.114			0.100			0.031			0.139
			(0.105)			(0.129)			(0.117)			(0.076)			(0.087)			(0.101)			(0.115)
High School Grad/GED or equivalent			0.166*			0.286**			0.034			0.056			0.111			0.037			0.147
			(0.099)			(0.122)			(0.112)			(0.072)			(0.082)			(0.096)			(0.109)
Some college or AA degree			0.135			**0.339*** **			0.074			-0.008			0.102			0.009			0.110
			(0.100)			**(0.124)**			(0.113)			(0.073)			(0.083)			(0.097)			(0.110)
College graduate or above			0.226**			0.329**			0.122			0.045			0.212**			0.050			0.108
			(0.108)			(0.133)			(0.122)			(0.078)			(0.090)			(0.105)			(0.119)
Smoking Status (Reference group is non-smokers)																					
Former smokers			-0.038			0.027			0.061			0.002			-0.027			0.056			-0.075
			(0.071)			(0.088)			(0.080)			(0.052)			(0.059)			(0.069)			(0.078)
Current Smokers			-0.167**			-0.129			-0.148			-0.090			-0.076			-0.129			-0.141
			(0.081)			(0.100)			(0.091)			(0.059)			(0.067)			(0.078)			(0.089)
Heavy Smokers			-0.072			-0.024			-0.050			0.020			-0.039			-0.077			0.008
			(0.066)			(0.081)			(0.074)			(0.048)			(0.054)			(0.063)			(0.072)
Observations	1,549	1,549	748	1,549	1,549	748	1,549	1,549	748	1,549	1,549	748	1,549	1,549	748	1,549	1,549	748	1,549	1,549	748
R-squared	0.042	0.162	0.266	0.050	0.109	0.206	0.012	0.092	0.169	0.056	0.207	0.304	0.066	0.207	0.305	0.039	0.206	0.279	0.026	0.218	0.291

Standard errors in parentheses

*** p<0.01, ** p<0.05, * p<0.1

Table 10. Chapter 6 - Hypothesis H3b Results

Variable	Total BMD			Lumbar BMD			Thoracic Spine BMD			Avg Arm BMD			Avg Leg BMD			Avg Rib BMD			Pelvis BMD		
Hypothesis	H3b1	H3b2	H3b3	H3b1	H3b2	H3b3	H3b1	H3b2	H3b3	H3b1	H3b2	H3b3	H3b1	H3b2	H3b3	H3b1	H3b2	H3b3	H3b1	H3b2	H3b3
Parity	-0.071***	-0.020**	0.014	-0.089***	-0.046***	-0.013	-0.041***	-0.023**	0.009	-0.062***	-0.017**	0.006	-0.076***	-0.040***	-0.008	-0.066***	-0.021**	-0.002	-0.061***	-0.015	0.014
	(0.009)	(0.009)	(0.015)	(0.010)	(0.011)	(0.019)	(0.009)	(0.010)	(0.017)	(0.006)	(0.007)	(0.011)	(0.007)	(0.008)	(0.013)	(0.008)	(0.009)	(0.015)	(0.009)	(0.010)	(0.017)
TL (age-adjusted)	0.029	0.046**	0.053**	0.021	0.032	0.052*	0.023	0.043**	0.064**	0.032**	0.044***	0.050***	0.022	0.041***	0.047**	-0.008	0.014	-0.005	0.010	0.040**	0.039
	(0.019)	(0.018)	(0.024)	(0.022)	(0.021)	(0.029)	(0.021)	(0.020)	(0.027)	(0.014)	(0.013)	(0.017)	(0.016)	(0.015)	(0.020)	(0.018)	(0.017)	(0.023)	(0.021)	(0.019)	(0.026)
Age		-0.017***	-0.031***		-0.014***	-0.028***		-0.010***	-0.023***		-0.014***	-0.023***		-0.014***	-0.023***		-0.017***	-0.023***		-0.019***	-0.030***
		(0.001)	(0.003)		(0.001)	(0.003)		(0.001)	(0.003)		(0.001)	(0.002)		(0.001)	(0.002)		(0.001)	(0.003)		(0.001)	(0.003)
BMI		0.015***	0.021***		0.008**	0.009		0.035***	0.042***		0.010***	0.011***		0.025***	0.034***		0.030***	0.030***		0.044***	0.052***
		(0.003)	(0.005)		(0.004)	(0.006)		(0.004)	(0.005)		(0.002)	(0.003)		(0.003)	(0.004)		(0.003)	(0.005)		(0.004)	(0.005)
Family Poverty Income Ratio			0.016			0.018			0.041**			0.016			0.018			-0.001			0.016
			(0.016)			(0.020)			(0.018)			(0.012)			(0.013)			(0.016)			(0.018)
# Weekly Drinks			0.008			0.007			0.009			0.012***			0.013***			0.001			0.012*
			(0.006)			(0.007)			(0.006)			(0.004)			(0.005)			(0.006)			(0.006)
Lifetime Estrogen Exposure			0.016***			0.016***			0.013***			0.011***			0.009***			0.004			0.013***
			(0.003)			(0.004)			(0.004)			(0.002)			(0.003)			(0.003)			(0.003)
Age at Menarche			0.018			-0.003			0.013			0.031***			0.027**			0.015			0.016
			(0.014)			(0.017)			(0.016)			(0.010)			(0.012)			(0.014)			(0.016)
Racialized Group (Reference group is white)																					
Black			0.240***			0.312***			0.135*			0.237***			0.094*			0.345***			0.291***
			(0.066)			(0.081)			(0.073)			(0.047)			(0.054)			(0.063)			(0.072)
Mexican			-0.140**			-0.143*			0.025			-0.145***			-0.190***			-0.126**			-0.149**
			(0.065)			(0.080)			(0.073)			(0.047)			(0.054)			(0.063)			(0.072)
Other Hispanic			-0.120			-0.138			-0.165			-0.156**			-0.187**			-0.032			-0.130
			(0.097)			(0.119)			(0.108)			(0.070)			(0.080)			(0.093)			(0.106)
Other (incl. multiracial)			0.080			0.030			0.300**			-0.141			0.036			-0.013			0.033
			(0.135)			(0.167)			(0.152)			(0.098)			(0.112)			(0.131)			(0.149)
Education (Reference group is <9th grade)																					
9-11th grade (Incl. 12th w/ no diploma)			0.116			0.305**			0.139			0.117			0.103			0.030			0.141
			(0.104)			(0.128)			(0.117)			(0.075)			(0.086)			(0.101)			(0.115)
High School Grad/GED or equivalent			0.159			0.279**			0.026			0.050			0.105			0.037			0.142
			(0.099)			(0.122)			(0.111)			(0.072)			(0.082)			(0.096)			(0.109)
Some college or AA degree			0.132			0.336***			0.071			-0.011			0.100			0.009			0.107
			(0.100)			(0.123)			(0.112)			(0.072)			(0.083)			(0.097)			(0.110)
College graduate or above			0.224**			0.328**			0.119			0.043			0.211**			0.050			0.107
			(0.108)			(0.133)			(0.121)			(0.078)			(0.090)			(0.105)			(0.119)
Smoking Status (Reference group is non-smokers)																					
Former smokers			-0.034			0.030			0.065			0.005			-0.024			0.056			-0.073
			(0.071)			(0.088)			(0.080)			(0.051)			(0.059)			(0.069)			(0.078)
Current Smokers			-0.164**			-0.125			-0.144			-0.087			-0.073			-0.129*			-0.138
			(0.081)			(0.100)			(0.091)			(0.058)			(0.067)			(0.078)			(0.089)
Heavy Smokers			-0.062			-0.013			-0.037			0.030			-0.029			-0.078			0.016
			(0.066)			(0.081)			(0.074)			(0.047)			(0.054)			(0.064)			(0.072)
Observations	1,549	1,549	748	1,549	1,549	748	1,549	1,549	748	1,549	1,549	748	1,549	1,549	748	1,549	1,549	748	1,549	1,549	748
R-squared	0.044	0.166	0.271	0.051	0.110	0.209	0.013	0.095	0.175	0.060	0.213	0.312	0.067	0.211	0.311	0.039	0.207	0.279	0.026	0.220	0.293

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

6.4.5 Limitations

Several limitations should be noted in interpreting these findings. First, the study does not formally test mediation using path analysis or structural equation modeling, limiting causal inference regarding LTL as an intermediary between reproduction and BMD. Given the lack of immediate evidence of mediation in our findings, however, we did not find this additional methodology pressing to incorporate here. Second, LTL and BMD were measured only once, constraining the ability to assess within-individual changes or temporal dynamics that might reveal stronger or lagged associations over time. Cross-sectional designs may obscure important life course relationships, especially in aging-related processes. Third, our maximally controlled models included a much larger number of variables, leading to much smaller sample sizes (e.g., women dropped from 1,626 to 1,006 in Hypothesis 1). This loss of power may underlie some instances where we have significant associations between LTL and BMD in our minimally controlled and medium models that are lost in this third and maximally controlled model. Future work here could focus on maintaining a larger sample size through restricting control variables or even imputation where feasible.

Fourth, LTL was assessed in peripheral blood using qPCR, a method that can be quite variable across labs and platforms. While qPCR is widely used in population studies, it lacks absolute precision, and methodological heterogeneity—such as sample storage, DNA extraction quality, and reference gene selection—may introduce noise (Lindrose et al., 2021; TRN Handbook, 2020). The NHANES documentation lacks full transparency on LTL assay quality control and technical replicability, complicating comparison to more recent standardized approaches. This could further complicate the issues with reduced sample size between models.

Further, LTL in blood may not reflect TL in bone-specific mesenchymal stem cells or osteoblasts and may miss important inter-individual variation in these other tissue types. Tissue specificity in aging markers remains a challenge for linking systemic biomarkers to localized outcomes like BMD.

Lastly, reproductive history was limited to parity, which may insufficiently capture the variability in physiological and energetic demands of reproduction. Life history theory emphasizes that reproductive costs vary across ecologies and individuals (Ellison, 2003, 2010). Key factors like lactation intensity, interbirth interval, and cumulative hormonal exposure were unavailable, yet likely moderate both telomere attrition and skeletal remodeling. As shown in the InterLACE consortium, reproductive trajectories differ substantially by cohort, education, and racial/ethnic background (InterLACE, 2018), suggesting unmeasured heterogeneity may underlie null findings.

6.5 DISCUSSION

Our analyses investigate whether blood TL, a key biomarker of biological aging, is associated with BMD in NHANES, a large, demographically diverse sample of U.S. adults. Specifically, we tested three hypotheses: 1) LTL is associated with BMD (total and regional), 2) higher parity will be associated with shorter LTL, and 3) LTL mediates the relationship between reproductive history (parity) and BMD in women. In partial support of our first hypothesis, we found that LTL was associated with BMD in multiple regions in our full sample, but these largely lost significance in our maximally controlled models. Contrary to our second hypothesis, parity was not a robust predictor of LTL (i.e., it was significant in the simplest LTL~parity model but not after including control variables). Lastly, contradicting our third hypothesis, while

we found associations between parity and BMD as well as LTL and BMD, including LTL in statistical models did not impact parity-BMD associations. In most cases, the parity coefficients remained exactly the same when including LTL. In sum, these findings suggest that while LTL may predict BMD, it is unlikely to underlie the connection between reproductive costs (e.g., parity) and BMD. Instead, it is more likely that they impact BMD through independent pathways.

Importantly, LTL showed all expected associations with demographic factors. For example, LTL was strongly associated with age and racialized group identity. Telomere attrition with age was evident across all relevant models, and non-Hispanic Black participants had longer LTL than non-Hispanic White participants. These patterns mirror demographic trends in BMD, where older adults have lower BMD, and Non-Hispanic Black adults tend to have higher bone mass than Non-Hispanic White adults (Araujo et al., 2007; Cauley et al., 2005; George et al., 2003; Nam et al., 2013; see also Chapter 5). However, these parallel patterns do not appear to result from group differences in LTL (i.e., LTL does not appear to mediate or moderate this relationship). The strength of the associations between these demographic factors and BMD did not appear to change with the inclusion (or exclusion) of LTL in the models (see Hypothesis 3 table).

Notably, in gender-stratified analyses, only women demonstrated significant associations between LTL and BMD, where longer LTL predicted greater BMD in the average arm and average leg BMD in the model controlling for age and BMI. While this supports our first hypothesis, the absence of strong associations in across more regions – and among men – suggests the LTL-BMD relationship may be site-specific and sex-specific.

We also tested whether LTL could help explain trade-offs between reproduction and skeletal maintenance in women. Contrary to our second and third hypotheses, parity was not associated with LTL and while it did predict BMD across regions, its effects weakened with the inclusion of our full suite of control variables and, importantly for our third hypothesis, did not change when LTL was included in the model. Adding LTL to the model did not alter the strength of the parity–BMD associations (e.g., parity $\beta = -0.089$ in the minimally adjusted model for with and without LTL). These findings provide no support for LTL as a mediator, moderator, or confounder for the relationship between reproductive history and skeletal aging.

Instead, LTL and parity, as measured here, may represent independent influences on bone health. One possibility is that cumulative reproductive exposure exerts short-term effects on bone mass that are later offset by recovery processes or masked by other aging-related changes. Another is that reproductive costs are primarily metabolic or hormonal rather than cellular in origin or that their cellular effects are not well captured by LTL as measured in peripheral blood. Lastly, as discussed in Paper 1, parity by itself may not effectively proxy the physiological costs of reproduction in humans. The energetic costs of breastfeeding alone are high enough that unmeasured variation in this behavior could easily confound any direct parity-BMD or even parity-LTL in this cohort.

It is important to note that our study (like most cohort studies of TL) measures LTL in DNA extracted from blood, and the majority of DNA in blood originates from white blood cells. While LTL is correlated across tissues (Demanelis et al., 2020), and LTL dynamics in blood are reflective of systemic aging processes in the individual, it is crucial to note the source of TL to determine, more specifically, how TL may connect to bone remodeling and BMD over the lifespan. In bone, shortened telomeres in osteoprogenitor cells are associated with impaired

osteoblastogenesis and increased marrow adipogenesis (Marie, 2014), contributing to the age-related decline in bone formation. Blood TL, however, originates from a different pool of stem cells than osteoprogenitor cells (hematopoietic vs mesenchymal stem cells). Thus, our small number of direct associations here may be due to the fact that we are measuring TL not in the osteoblasts but in the blood, and the association between blood TL and osteoblast TL (although correlated) may have sufficient variation to result in little to no association between BMD and LTL. However, both LTL and BMD are impacted by chronic inflammation, so it is interesting to see such a lack of associations with this.

This chapter contributes to a growing recognition that biological aging is not a singular construct, but rather the confluence of multiple domain-specific systems that, although they likely influence each other, also occur independently. LTL and BMD each reflect important domains of aging: cellular and skeletal, respectively. Demographic factors such as age and race structure both traits, perhaps through parallel inherited or environmental mechanisms. The LTL associations with BMD only in the arm and leg regions among women, suggests that future research should examine regional specificity, sex differences, and alternative senescence markers more directly tied to osteoblast and osteocyte function. This finding is particularly interesting, as regions with greater relative trabecular bone may exhibit stronger relationships between LTL and BMD, since these regions may change more rapidly with age compared to cortical bone. While bones in the legs may have greater relative trabecular bone, this is not quite the case with the arms.

While we failed to find evidence that blood TL mediates the relationship between reproduction and BMD, life history trade-offs remain a valuable framework for understanding bone aging. Our findings suggest that the biological cost of reproduction on bone may operate

independently of LTL, may not be measurable in BMD, or may only be detectable under specific conditions of stress or nutritional strain that are not fully captured in NHANES data. These are each important – and testable – takeaways for the future study of bone aging and its relationship to the hallmarks of aging, as well as its role in human evolution and implications for population health.

6.6 CONCLUSION

This chapter explores the mechanisms of skeletal aging by examining how and when LTL, a molecular biomarker of cellular senescence, relates to BMD and whether it could underlie age-related and reproductive-related changes in BMD. Shorter telomere lengths correlated with reduced BMD across multiple skeletal sites, providing initial evidence that systemic cellular aging plays a role in skeletal health. Interestingly, these associations were strongest and most apparent in women, suggesting important gender-dependent roles for cellular aging in skeletal integrity with age. Importantly, these associations existed independently of parity as it was not strongly related to LTL and was independently associated with BMD. This highlights the complementary nature of direct reproductive costs and cellular aging on bone health and emphasizes an exciting new direction that we did not consider in before these analyses: that the role of telomeres in bone health shifts based on gender or sex. Unfortunately, the variables we had prepared for the current analyses do not allow us to dig further into what could drive this difference.

It is important to note our study's limitations. Telomere measurement, while increasingly standardized, remains methodologically challenging due to variability in PCR assay performance, sample quality, and assay repeatability (Lindrose et al., 2021; Telomere Research

Network Handbook). The predominantly cross-sectional design further restricts causal interpretations, as the longitudinal dynamics of telomeres and their direct impacts on bone loss remain unclear. Additionally, TL measurements from blood might not precisely reflect the telomere dynamics of bone-specific cell populations. Future research should aim for longitudinal designs with newer standards of TL measurement, larger and more diverse populations, and validation across laboratories and methods (i.e., validating qPCR measured TL to Southern Blot) to ensure robust replicability and reproducibility of TL measurement.

Future research should aim to reproduce our gender-specific TL-BMD associations, preferably with more longitudinal data on hormonal exposure, reproductive history, and health history more broadly (as well as clearer TL data and larger sample sizes). Broadly, we feel our findings here emphasize that comprehensive frameworks combining molecular aging, reproductive ecology, and socio-environmental determinants offer promising avenues for advancing understanding and developing practical interventions to promote skeletal health across diverse human populations alongside improving our understanding of the evolution of bone health over the life course.

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Chapter 7: CONCLUSIONS AND FUTURE DIRECTIONS

This dissertation explores the dynamics of bone remodeling, its adaptive responses to reproduction and aging, and cellular mechanisms that influence them to connect life history constraints to skeletal health. Conducting analyses of large-scale, publicly available data from the US NHANES dataset, each chapter contributes distinct but interconnected insights, collectively enhancing our understanding of human skeletal adaptation through evolutionary, demographic, and molecular perspectives.

7.1 Parity and Bone Mineral Density

Chapter 4 examines the relationship between reproductive history and bone health, focusing on the association between parity and BMD across various anatomical regions. Key findings revealed that reproductive events have nuanced and region-specific effects on the maternal skeleton, supporting life history theory predictions. High parity was associated with lower BMD, particularly in regions rich in trabecular bone (e.g., lumbar spine), emphasizing that the metabolic demands of reproduction may preferentially affect skeletal areas prone to higher metabolic activity, remodeling, and greater resorption. Conversely, regions subjected regularly to mechanical loading, such as the femoral neck, appeared more resistant to parity-related bone loss, suggesting a protective effect of habitual mechanical strain.

This chapter highlights how life history trade-offs between reproduction and somatic maintenance are translated into bone health and aging. It highlights the evolutionary pressures shaping maternal skeletal physiology and points to the implications of reproductive strategies on skeletal aging trajectories. This research has clinical relevance by illustrating how reproductive histories can influence BMD, which, in turn, can inform the development of individualized

osteoporosis risk profiles. Future research should prioritize longitudinal studies examining cumulative reproductive impacts, interbirth intervals, and postpartum recovery periods to refine our understanding of skeletal resilience and vulnerability through reproduction.

7.2 BMD Variation Across Anatomical Regions and Life Course

Chapter 5 expands the scope beyond reproductive costs and parity to provide a more comprehensive analysis of demographic and lifestyle factors, as well as their associations with BMD variation across anatomical regions. Crucially, this chapter demonstrates that mechanical loading alone is insufficient to buffer against age-related BMD loss across skeletal sites. Weight-bearing regions and non-weight-bearing regions showed similar age-related declines in BMD overall, although this pattern varied by gender. Women showed a steeper age-related decline in BMD in non-WBRs; men showed comparable negative associations between regions. Non-Hispanic Blacks had higher BMD in every region than non-Hispanic Whites. Socioeconomic status and heavy smoking were strong predictors of BMD. Notably, increased sedentary time was associated exclusively with lower BMD in non-WBRs (all $p < 0.001$). These findings strongly emphasized how structural inequities and modifiable risk behaviors critically shape skeletal aging processes.

This chapter's findings highlight the importance of integrating socioeconomic environments and lifestyle behaviors with mechanical loading when understanding bone health dynamics with age. The intersectional investigation of biomechanical, demographic, and social determinants of health highlights the need for targeted public health strategies, emphasizing a holistic approach to preventing age-related bone fragility. Future research should further investigate the interplay between systemic inequalities, behavioral health interventions, and their

long-term efficacy in mitigating skeletal aging. Lastly, mechanical loading is expected to buffer against bone loss in weight-bearing regions; however, we found no strong evidence for this in our cohort. This may, in part, be due to the ability of bone to respond and remodel to mechanical loading, which likely decreases with age, highlighting another promising avenue for future research: investigating how the cells responsible for remodeling (e.g., osteoclasts, osteoblasts) change with age.

7.3 Telomere Length and Biomarkers of Aging in Bone Remodeling

In Chapter 6, my dissertation integrated cellular aging into my study of bone health by examining telomere length (TL), a molecular biomarker of cellular aging, in relation to BMD in a separate NHANES cohort (1999-2002) that contained DXA and TL data. Motivated broadly by previous studies positing links between cellular senescence and bone remodeling, we found that: 1) TL predicted BMD in two regions (average arm and average leg) in women only; 2) parity did not predict TL; and 3) TL and parity had independent associations with BMD.

Importantly, associations between parity and BMD from Chapters 4 and 5 were reproduced in this separate NHANES cohort (e.g., Non-Hispanic Blacks had higher BMD than non-Hispanic whites). While demographic associations with TL paralleled the demographic associations with BMD, TL did not appear to mediate, moderate, or influence the associations between these demographic factors and BMD (similarly to how it did not influence parity-BMD associations).

Connecting TL to BMD in NHANES expands our understanding of bone loss beyond the conventional framework of mechanical loading and calcium homeostasis, integrating molecular biology into the life history narrative of skeletal aging. A key question for future studies to

investigate is why TL-BMD associations appeared in women-only analyses but not men-only analyses. This difference could have implications for sex differences in risk factors of osteoporosis and other bone-related disorders and diseases that become more likely with older age. More generally, the relationships between cellular aging and bone health would benefit from longitudinal studies that could better untangle the relationships between telomere attrition and reproductive history, as well as more detailed environmental and genetic factors.

7.4 Summary Conclusion

Collectively, my three analytical chapters form a cohesive narrative that underscores the complex adaptive processes governing bone health throughout human life history. This dissertation connects anthropological theory, evolutionary biology, and epidemiological methods to provide a comprehensive and nuanced view of bone remodeling in humans, with important implications for a better understanding of human adaptation, aging, and health throughout the life course.

Life history theory is at the core of my hypotheses, focusing on the constraints and trade-offs inherent in human reproductive strategies and their consequences for somatic maintenance, particularly for skeletal adaptation and aging. This work was also motivated by evolutionary medicine ideas that contextualize contemporary skeletal pathologies as outcomes of deep evolutionary processes shaped by adaptations and mismatches with modern lifestyles. From an evolutionary perspective, skeletal fragility and osteoporosis are not merely diseases of modernity but rather reflect evolutionary compromises that optimized for reproductive success rather than late-life skeletal resilience.

Mechanotransduction, biomechanical loading, and cellular aging each represent critical axes of skeletal adaptation. Mechanical loading appears paramount in promoting skeletal robustness throughout life, yet its effectiveness wanes with age and is variably influenced by socio-demographic factors and lifestyle choices. Telomere length, as an accessible molecular biomarker of biological aging, emerges as a potential mediator connecting cellular senescence and aging with skeletal integrity.

The implications of these findings extend beyond anthropological theory into clinical and public health domains, advocating for personalized, life-course-oriented approaches to the prevention and management of osteoporosis. Public health strategies derived from these insights may prioritize early-life interventions that promote mechanical loading optimal nutrition and address social determinants of health to maximize peak bone mass and slow age-related bone loss.

7.5 Future Directions

My future research directions will prioritize comprehensive, biocultural approaches to expand understandings of human locomotion and reproduction and their impact on bone health and aging. Longitudinal analyses are particularly crucial, as they can clarify causal relationships and temporal dynamics linking reproductive events, mechanical loading, cellular aging, and bone health. Such studies could track individuals from early to middle and late adulthood, providing invaluable data on how reproductive timing, frequency, and postpartum recovery periods influence skeletal integrity throughout life and what mechanisms underlie these influences (e.g., hormonal changes, molecular dynamics).

Cross-cultural comparisons represent another critical area of inquiry. Investigating how different reproductive strategies, nutritional environments, and activity patterns across diverse

populations influence skeletal aging can help distinguish the ultimate and context-specific mechanisms underlying bone health. These studies would benefit from collaborative frameworks that integrate the work of bioarcheologists, epidemiologists, and public health researchers to facilitate robust comparative analyses that incorporate ecological and cultural variability.

Advances in molecular biology and genetics also present significant opportunities for future research. Identifying the genetic determinants and molecular pathways involved in telomere maintenance, cellular senescence, and bone remodeling could lead to the development of predictive biomarkers and targeted therapies. Genome-wide association studies (GWAS) and transcriptomic analyses can identify novel genes and regulatory mechanisms associated with healthy bone remodeling and aging, potentially guiding precision medicine approaches to skeletal health.

The use of advanced imaging and microstructural analyses will also significantly enhance our investigative capacity by providing more nuanced outcome variables with more specific connections to bone functional adaptation. High-resolution peripheral quantitative computed tomography and magnetic resonance imaging can reveal changes in bone microarchitecture at an unprecedented resolution, helping to identify early signs of structural deterioration and test interventions designed to enhance microdamage repair or mechanical responsiveness. By embracing the need for interdisciplinary research prioritization, future studies will substantially enhance our theoretical and practical understanding of skeletal health, promoting strategies to improve not only our knowledge of our evolutionary history but also of longevity and quality of life across human populations.

APPENDICES

APPENDIX A: Chapter 3 Supplementary Information

Figure 4. Sample Hologic DXA Report

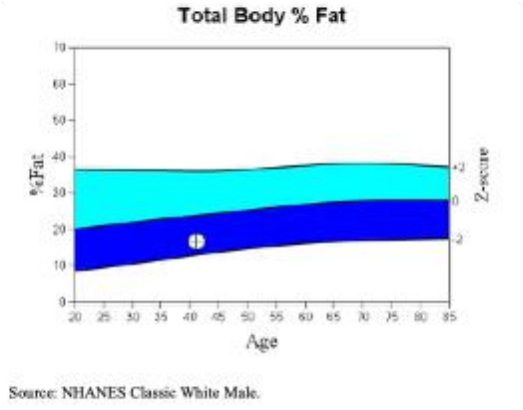
Hologic, Inc

250 Campus Drive
Marlborough, MA 01752

Telephone: 1-508-263-2471 E-Mail: BSHSalesSupportUS@hologic.com

Name: Doe, John	Sex: Male	Height: 71.5 in
Patient ID: 65489	Ethnicity: White	Weight: 189.5 lb
DOB: May 05, 1968		Age: 41

Images not for diagnostic use



BMI has some limitations and an actual diagnosis of overweight or obesity should be made by a health professional. Obesity is associated with heart disease, certain types of cancer, type 2 diabetes, and other health risks. The higher a person's BMI is above 25, the greater their weight-related risks.

Body Composition Results

Region	Fat Mass (lb)	Lean + BMC (lb)	Total Mass (lb)	% Fat	%Fat Percentile YN	%Fat Percentile AM
L Arm	1.66	8.48	10.14	16.4	41	24
R Arm	1.81	8.78	10.59	17.1	43	25
Trunk	13.93	78.41	92.34	15.1	24	8
L Leg	5.63	26.18	31.81	17.7	25	18
R Leg	6.33	26.46	32.79	19.3	32	24
Subtotal	29.35	148.31	177.66	16.5	26	11
Head	2.36	9.53	11.89	19.9		
Total	**31.72**	**157.84**	**189.56**	**16.7**	**26**	**11**
Android (A)	2.43	11.19	13.62	17.8		
Gynoid (G)	6.27	24.33	30.61	20.5		

Scan Date: July 09, 2009 ID: A0709090A
Scan Type: a Whole Body
Analysis: October 07, 2019 09:50 Version 13.6.0.7
Auto Whole Body Fan Beam
Operator:
Model: Discovery A (S/N 45539)
Comment:

Adipose Indices

Measure	Result	Percentile YN	Percentile AM
Total Body % Fat	**16.7**	**26**	**11**
Fat Mass/Height² (kg/m²)	4.36	34	18
Android/Gynoid Ratio	0.87		
% Fat Trunk/% Fat Legs	0.82	30	11
Trunk/Limb Fat Mass Ratio	0.90	36	12
Est. VAT Mass (g)	301		
Est. VAT Volume (cm³)	325		
Est. VAT Area (cm²)	62.4		

Lean Indices

Measure	Result	Percentile YN	Percentile AM
Lean/Height² (kg/m²)	20.8	67	58
Appen. Lean/Height² (kg/m²)	9.16	56	51

Est. VAT = Estimated Visceral Adipose Tissue
YN = Young Normal
AM = Age Matched

HOLOGIC®

Figure 5. NHANES Mobile Examination Center Example

Figure 6. Hologic Densitometer Discovery A System

Figure 7. Hologic QDR 4500/A DXA System

APPENDIX B: Chapter 4 Supplementary Information

Table 11. Chapter 4 - Supplementary Data

Variable	n=	Sample Mean or %	SD	Min	Max	Total BMD Sample Mean or %	SD	Min	Max	Total Femur Sample Mean or %	SD	Min	Max
Age in years	5144	39.7	13.4	20	79	37.1	11.2	20	59	43.3	15.1	20	79
Number of Deliveries		1.8	1.6	0	11	1.7	1.6	0	10	2.1	1.7	0	11
Nulliparous	1431	27.8%				32.2%				22.2%			
Mass (kg)		72.1	14.9	39.6	133.3	71.6	15.1	39.6	120.1	72.0	14.4	40.2	120.1
Height (cm)		161.4	7.0	135	188	161.3	7.0	135	184	161.3	7.0	140	188
BMI (kg/m^2)		27.7	5.3	18.5	40	27.5	5.4	18.5	40	27.6	5.1	18.5	40
Racialized Group													
Non-Hispanic White	1945	37.8%				34.8%				42.4%			
Non-Hispanic Black	1086	21.1%				20.3%				19.5%			
Mexican-American	858	16.7%				14.8%				19.5%			
Non-Hispanic Other	572	11.1%				10.9%				12.0%			
Other Incl. Multi-Racial	683	13.3%				19.1%				6.5%			
Highest Level of Education													
Less Than 9th Grade	330	6.4%				4.7%				8.3%			
9-11th Grade (Incl. 12th Grade w/ No Diploma)	605	11.8%				9.1%				14.6%			
High School Grad/GED or Equivalent	1027	20.0%				18.4%				21.9%			
Some College or AA Degree	1764	34.3%				36.9%				31.9%			
College Graduate or Above	1418	27.6%				31.0%				23.3%			
Family Poverty Income Ratio													
<1.3 (low-income)	1615	31.4%				31.1%				30.7%			
1.3-3.4 (middle-income)	1913	37.2%				36.3%				38.4%			
3.5-5 (high-income)	1616	31.4%				32.6%				31.0%			
Smoking Status													
Non-Smoker	3721	72.3%				74.1%				70.3%			
Former Smoker	485	9.4%				9.3%				9.5%			
Current Smoker	572	11.1%				8.9%				9.4%			
Heavy Smoker	466	9.1%				7.7%				10.8%			
# Weekly Drinks		2.0	4.9	0	84	2.0	4.8	0	84	1.9	4.9	0	84
Lifetime Estrogen Exposure		24.2	10.4	3	67	23.0	9.9	3	47	26.2	10.9	4	67
Age at Menarche (years)		12.7	1.7	6	21	12.7	1.8	6	21	12.8	1.7	6	19
Sedentary Hours/Day		5.8	3.4	0.5	20	6.3	3.4	0.5	20	5.2	3.3	0.5	20

Variable	Total Spine Sample Mean or %	SD	Min	Max	Lumbar Spine Sample Mean or %	SD	Min	Max	Thoracic Spine Sample Mean or %	SD	Min	Max
Age in years	41.9	14.3	20	79	38.8	12.7	20	79	37.1	11.2	20	59
Number of Deliveries	2.0	1.7	0	11	1.8	1.6	0	11	1.7	1.6	0	11
Nulliparous	22.9%				28.6%				32.2%			
Mass (kg)	71.9	14.5	40.2	117.6	71.9	14.9	39.6	133.3	71.8	15.2	39.6	133.3
Height (cm)	161.4	7.0	140	184	161.4	7.0	135	188	161.4	7.0	135	188
BMI (kg/m^2)	27.6	5.2	18.5	40	27.6	5.3	18.5	40	27.5	5.4	18.5	40
Racialized Group												
Non-Hispanic White	41.5%				37.2%				33.9%			
Non-Hispanic Black	19.5%				21.0%				22.1%			
Mexican-American	20.7%				17.0%				14.4%			
Non-Hispanic Other	11.8%				10.9%				10.4%			
Other Incl. Multi-Racial	6.5%				13.9%				19.2%			
Highest Level of Education												
Less Than 9th Grade	8.3%				6.2%				4.7%			
9-11th Grade (Incl. 12th Grade w/ No Diploma)	14.6%				11.5%				9.1%			
High School Grad/GED or Equivalent	21.6%				19.7%				18.4%			
Some College or AA Degree	31.9%				34.5%				36.6%			
College Graduate or Above	23.7%				28.2%				31.2%			
Family Poverty Income Ratio												
<1.3 (low-income)	31.1%				31.5%				31.4%			
1.3-3.4 (middle-income)	37.9%				36.9%				36.5%			
3.5-5 (high-income)	31.0%				31.5%				32.1%			
Smoking Status												
Non-Smoker	71.6%				73.1%				74.5%			
Former Smoker	8.9%				9.2%				9.2%			
Current Smoker	9.5%				9.2%				9.0%			
Heavy Smoker	10.0%				8.5%				7.3%			
# Weekly Drinks	1.9	5.0	0	84	2.0	4.9	0	84	2.0	4.8	0	84
Lifetime Estrogen Exposure	25.5	10.7	4	67	23.8	10.2	3	67	23.0	9.9	3	47
Age at Menarche (years)	12.7	1.7	6	19	12.7	1.7	6	20	12.7	1.8	6	20
Sedentary Hours/Day	5.1	3.4	0.5	20	5.8	3.5	0.5	20	6.3	3.4	0.5	20

Variable	Femoral Neck, Trochanter, and Intertrochanter BMD Sample Mean or %	SD	Min	Max	Average Arm BMD Sample Mean or %	SD	Min	Max	Average Leg BMD Sample Mean or %	SD	Min	Max	Average Rib BMD Sample Mean or %	SD	Min	Max	Pelvis BMD Sample Mean or %	SD	Min	Max
Age in years	43.3	15.1	20	79	37.2	11.2	20	59	37.1	11.2	20	59	37.1	11.2	20	59	37.1	11.2	20	59
Number of Deliveries	2.1	1.7	0	11	1.7	1.6	0	11	1.7	1.6	0	11	1.7	1.6	0	11	1.7	1.6	0	11
Nulliparous	22.2%				32.2%				32.1%				32.2%				32.2%			
Mass (kg)	72.0	14.4	40.2	120.1	71.7	15.1	39.6	133.3	71.7	15.1	39.6	120.1	71.8	15.2	39.6	133.3	71.8	15.2	39.6	133.3
Height (cm)	161.3	7.0	140	188	161.4	7.0	135	188	161.4	7.0	135	184.3	161.4	7.0	135	188	161.4	7.0	135	188
BMI (kg/m^2)	27.6	5.1	18.5	40	27.5	5.4	18.5	40	27.5	5.4	18.5	40	27.5	5.4	18.5	40	27.5	5.4	18.5	40
Racialized Group																				
Non-Hispanic White	42.4%				34.3%				34.1%				33.9%				33.9%			
Non-Hispanic Black	19.5%				21.5%				21.8%				22.1%				22.1%			
Mexican-American	19.5%				14.6%				14.5%				14.4%				14.4%			
Non-Hispanic Other	12.0%				10.8%				10.6%				10.4%				10.4%			
Other Incl. Multi-Racial	6.5%				18.7%				19.0%				19.2%				19.2%			
Highest Level of Education																				
Less Than 9th Grade	8.3%				4.7%				4.7%				4.7%				4.7%			
9-11th Grade (Incl. 12th Grade w/ No Diploma)	14.6%				9.2%				9.1%				9.1%				9.1%			
High School Grad/GED or Equivalent	21.9%				18.4%				18.2%				18.4%				18.4%			
Some College or AA Degree	31.9%				36.9%				36.8%				36.6%				36.6%			
College Graduate or Above	23.3%				30.8%				31.2%				31.2%				31.2%			
Family Poverty Income Ratio																				
<1.3 (low-income)	30.7%				31.5%				31.3%				31.4%				31.4%			
1.3-3.4 (middle-income)	38.4%				36.2%				36.5%				36.5%				36.5%			
3.5-5 (high-income)	31.0%				32.3%				32.2%				32.1%				32.1%			
Smoking Status																				
Non-Smoker	70.3%				74.0%				74.3%				74.5%				74.5%			
Former Smoker	9.5%				9.1%				9.2%				9.2%				9.2%			
Current Smoker	9.4%				9.2%				8.9%				9.0%				9.0%			
Heavy Smoker	10.8%				7.7%				7.5%				7.3%				7.3%			
# Weekly Drinks	1.9	4.9	0	84	2.0	4.9	0	84	2.0	4.8	0	84	2.0	4.8	0	84	2.0	4.8	0	84
Lifetime Estrogen Exposure	26.2	10.9	4	67	23.0	9.9	3	47	23.0	9.9	3	47	23.0	9.9	3	47	23.0	9.9	3	47
Age at Menarche (years)	12.8	1.7	6	19	12.7	1.8	6	21	12.7	1.8	6	21	12.7	1.8	6	20	12.7	1.8	6	20
Sedentary Hours/Day	5.2	3.3	0.5	20	6.3	3.4	0.5	20	6.3	3.4	0.5	20	6.3	3.4	0.5	20	6.3	3.4	0.5	20

APPENDIX C: Chapter 5 Supplementary Information

Table 12. BMD and Covariate Associations by Anatomical Region. Total Sample

Anatomical Region			Weight-Bearing	Non-WeightBearing	Total BMD	Total Femur	Total Spine	Lumbar Spine	Thoracic Spine	Femoral Neck	Trochanter	Intertrochanter	Avg Arm	Avg Leg	Avg Rib	Pelvis
Total Sample	Observations		6,414	6,315	6,222	5,020	4,215	10,602	6,548	5,020	5,020	5,020	6,534	6,414	6,548	6,548
Gender (Men)	*ref. Women*	β	**0.741***	**0.778***	**0.313***	**0.413***	**-0.570***	**-0.441***	**-0.170***	**0.319***	**0.323***	**0.431***	**0.892***	**0.741***	**0.570***	0.161
			(0.051)	(0.050)	(0.056)	(0.060)	(0.063)	(0.046)	(0.059)	(0.063)	(0.066)	(0.059)	(0.045)	(0.051)	(0.059)	(0.058)
		p=	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.004	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.006
BMI (kg/m^2)		β	**0.029***	**0.024***	**0.021***	**0.061***	**0.037***	**0.010***	**0.026***	**0.058***	**0.053***	**0.059***	**0.028***	**0.029***	**0.015***	**0.045***
			(0.002)	(0.001)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.002)	(0.001)	(0.002)	(0.002)	(0.002)
		p=	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Racialized Group	*(ref. Non-Hispanic White)*															
	Non-Hispanic Black	β	**0.300***	**0.373***	**0.418***	**0.336***	**0.243***	**0.376***	**0.334***	**0.462***	**0.241***	**0.330***	**0.212***	**0.300***	**0.546***	**0.320***
			(0.021)	(0.020)	(0.023)	(0.027)	(0.028)	(0.020)	(0.024)	(0.029)	(0.030)	(0.027)	(0.018)	(0.021)	(0.024)	(0.023)
		p=	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Mexican-American	β	**-0.175***	**-0.126***	**-0.120***	-0.039	**-0.211***	**-0.171***	0.010	-0.037	**-0.170***	0.007	**-0.188***	**-0.175***	-0.025	-0.046
			(0.025)	(0.024)	(0.027)	(0.030)	(0.031)	(0.023)	(0.029)	(0.032)	(0.033)	(0.030)	(0.022)	(0.025)	(0.029)	(0.029)
		p=	<0.001	<0.001	<0.001	0.197	<0.001	<0.001	0.741	0.249	<0.001	0.804	<0.001	<0.001	0.386	0.105
	Non-Hispanic Other	β	**-0.162***	**-0.122***	**-0.094***	0.024	**-0.140***	**-0.103***	-0.004	0.037	-0.031	0.058	**-0.188***	**-0.162***	-0.023	**-0.098***
			(0.027)	(0.026)	(0.029)	(0.034)	(0.036)	(0.026)	(0.031)	(0.036)	(0.038)	(0.034)	(0.024)	(0.027)	(0.031)	(0.031)
		p=	<0.001	<0.001	0.001	0.487	<0.001	<0.001	0.896	0.306	0.418	0.085	<0.001	<0.001	0.461	0.002
	Other Incl. Multi-Racial	β	**-0.151***	**-0.208***	**-0.119***	-0.107	**-0.157***	**-0.120***	-0.006	-0.078	**-0.143***	-0.082	**-0.249***	**-0.151***	**-0.128***	**-0.118***
			(0.021)	(0.021)	(0.023)	(0.041)	(0.043)	(0.023)	(0.024)	(0.043)	(0.045)	(0.040)	(0.019)	(0.021)	(0.025)	(0.024)
		p=	<0.001	<0.001	<0.001	0.009	<0.001	<0.001	0.796	0.069	0.001	0.04	<0.001	<0.001	<0.001	<0.001
Educational Attainment	*(ref. Less than 9th Grade)*															
	9-11th Grade (Incl. 12th Grade w/ No Diploma)	β	0.080	0.093	**0.145***	-0.095	0.084	**0.126***	0.101	-0.103	-0.075	-0.103	0.048	0.080	0.116	0.078
			(0.040)	(0.039)	(0.044)	(0.042)	(0.044)	(0.035)	(0.046)	(0.044)	(0.046)	(0.041)	(0.035)	(0.040)	(0.046)	(0.045)
		p=	0.047	0.017	0.001	0.023	0.055	<0.001	0.027	0.02	0.105	0.013	0.175	0.047	0.011	0.087
	High School Grad/GED or Equivalent	β	0.073	0.045	0.104	-0.065	0.103	**0.126***	0.085	-0.102	-0.027	-0.072	0.027	0.073	0.052	0.064
			(0.038)	(0.037)	(0.041)	(0.040)	(0.042)	(0.033)	(0.043)	(0.042)	(0.044)	(0.040)	(0.034)	(0.038)	(0.043)	(0.043)
		p=	0.054	0.219	0.011	0.105	0.015	<0.001	0.05	0.016	0.548	0.07	0.419	0.054	0.234	0.136
	Some College or AA Degree	β	**0.120***	0.059	**0.127***	-0.085	**0.114***	**0.156***	0.108	**-0.118***	-0.076	-0.080	0.019	**0.120***	0.090	0.095
			(0.037)	(0.036)	(0.041)	(0.041)	(0.043)	(0.033)	(0.043)	(0.043)	(0.045)	(0.040)	(0.033)	(0.037)	(0.043)	(0.043)
		p=	0.001	0.107	0.002	0.037	0.008	<0.001	0.012	0.006	0.088	0.046	0.566	0.001	0.037	0.025
	College Graduate or Above	β	**0.164***	0.027	**0.166***	-0.006	0.122	**0.160***	0.099	-0.043	0.004	-0.009	-0.004	**0.164***	0.049	**0.116***
			(0.039)	(0.039)	(0.043)	(0.044)	(0.046)	(0.036)	(0.045)	(0.047)	(0.049)	(0.044)	(0.035)	(0.039)	(0.046)	(0.045)
		p=	<0.001	0.477	<0.001	0.889	0.008	<0.001	0.029	0.351	0.929	0.834	0.917	<0.001	0.282	0.01
Family Poverty Income Ratio		β	**0.032***	**0.023***	**0.027***	**0.025***	**0.019***	**0.024***	**0.018***	0.016	**0.027***	**0.024***	**0.023***	**0.032***	**0.022***	**0.026***
			(0.005)	(0.005)	(0.006)	(0.007)	(0.007)	(0.005)	(0.006)	(0.007)	(0.008)	(0.007)	(0.005)	(0.005)	(0.006)	(0.006)
		p=	<0.001	<0.001	<0.001	<0.001	0.009	<0.001	0.002	0.028	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Smoking Status	*(ref. Non-Smokers)*															
	Former Smoker	β	0.012	0.020	0.005	**-0.100***	-0.065	-0.041	0.008	-0.059	**-0.129***	**-0.103***	0.045	0.012	0.002	-0.010
			(0.023)	(0.023)	(0.025)	(0.031)	(0.033)	(0.023)	(0.027)	(0.033)	(0.034)	(0.031)	(0.021)	(0.023)	(0.027)	(0.026)
		p=	0.595	0.377	0.842	0.001	0.05	0.071	0.754	0.076	<0.001	0.001	0.03	0.595	0.934	0.706
	Current Smoker	β	0.032	0.065	0.018	**-0.093***	-0.034	-0.025	-0.032	-0.045	**-0.137***	-0.080	**0.090***	0.032	0.029	0.005
			(0.024)	(0.024)	(0.027)	(0.033)	(0.034)	(0.024)	(0.028)	(0.035)	(0.036)	(0.032)	(0.021)	(0.024)	(0.028)	(0.028)
		p=	0.191	0.006	0.51	0.004	0.311	0.286	0.252	0.188	<0.001	0.013	<0.001	0.191	0.3	0.866
	Heavy Smoker	β	0.021	0.066	0.021	**-0.148***	-0.029	-0.010	-0.037	**-0.099***	**-0.186***	**-0.135***	**0.111***	0.021	0.012	0.010
			(0.027)	(0.026)	(0.029)	(0.031)	(0.033)	(0.025)	(0.030)	(0.033)	(0.034)	(0.031)	(0.023)	(0.027)	(0.031)	(0.030)
		p=	0.432	0.011	0.466	<0.001	0.375	0.696	0.225	0.003	<0.001	<0.001	<0.001	0.432	0.687	0.732
# Weekly Drinks		β	**0.004***	**0.004***	**0.003***	**0.006***	**0.005***	**0.005***	0.001	**0.006***	**0.008***	**0.005***	**0.005***	**0.004***	0.002	0.002
			(0.001)	(0.001)	(0.001)	(0.001)	(0.002)	(0.001)	(0.001)	(0.002)	(0.002)	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
		p=	0.001	<0.001	0.009	<0.001	0.001	<0.001	0.625	<0.001	<0.001	<0.001	<0.001	0.001	0.081	0.064
Sedentary Hours/Day		β	-0.005	**-0.011***	**-0.007***	-0.006	-0.002	-0.004	**-0.008***	-0.007	-0.008	-0.005	**-0.011***	-0.005	**-0.009***	-0.006
			(0.002)	(0.002)	(0.002)	(0.003)	(0.003)	(0.002)	(0.003)	(0.003)	(0.003)	(0.003)	(0.002)	(0.002)	(0.003)	(0.003)
		p=	0.038	<0.001	0.004	0.035	0.558	0.08	0.002	0.034	0.018	0.08	<0.001	0.038	<0.001	0.019

Standard errors in parentheses. ***indicates significance (p≤0.004)**

Table 13. BMD and Covariate Associations by Anatomical Region. Women Only Subgroup

Anatomical Region			Weight-Bearing	Non-WeightBearing	Total BMD	Total Femur	Total Spine	Lumbar Spine	Thoracic Spine	Femoral Neck	Trochanter	Intertrochanter	Avg Arm	Avg Leg	Avg Rib	Pelvis
Women Only	Observations		2,935	2,785	2,814	2,278	1,959	4,762	2,874	2,278	2,278	2,278	2,931	2,935	2,874	2,874
BMI (kg/m^2)		β	**0.039***	**0.031***	**0.022***	**0.069***	**0.044***	**0.017***	**0.024***	**0.064***	**0.065***	**0.065***	**0.032***	**0.039***	**0.025***	**0.040***
			(0.002)	(0.002)	(0.003)	(0.003)	(0.003)	(0.002)	(0.003)	(0.003)	(0.003)	(0.003)	(0.002)	(0.002)	(0.003)	(0.003)
		p=	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Racialized Group	*(ref. Non-Hispanic White)*															
	Non-Hispanic Black	β	**0.193***	**0.393***	**0.370***	**0.209***	**0.163***	**0.259***	**0.177***	**0.357***	0.127	**0.200***	**0.249***	**0.193***	**0.521***	**0.216***
			(0.034)	(0.035)	(0.037)	(0.042)	(0.044)	(0.031)	(0.039)	(0.042)	(0.046)	(0.041)	-0.033	(0.034)	(0.039)	(0.036)
		p=	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.006	<0.001	<0.001	<0.001	<0.001	<0.001
	Mexican-American	β	**-0.251***	**-0.128***	-0.117	-0.075	**-0.275***	**-0.211***	-0.013	-0.087	**-0.193***	-0.010	**-0.258***	**-0.251***	0.038	-0.043
			(0.041)	(0.041)	(0.043)	(0.045)	(0.046)	(0.035)	(0.047)	(0.045)	(0.049)	(0.044)	(0.040)	(0.041)	(0.047)	(0.044)
		p=	<0.001	0.002	0.007	0.094	<0.001	<0.001	0.775	0.055	<0.001	0.813	<0.001	<0.001	0.411	0.327
	Non-Hispanic Other	β	**-0.282***	**-0.154***	**-0.130***	-0.054	**-0.237***	**-0.168***	-0.050	-0.053	-0.110	-0.007	**-0.280***	**-0.282***	-0.013	**-0.172***
			(0.043)	(0.043)	(0.045)	(0.050)	(0.053)	(0.039)	(0.049)	(0.051)	(0.055)	(0.050)	(0.041)	(0.043)	(0.049)	(0.046)
		p=	<0.001	<0.001	0.004	0.283	<0.001	<0.001	0.313	0.294	0.048	0.884	<0.001	<0.001	0.793	<0.001
	Other Incl. Multi-Racial	β	**-0.234***	**-0.279***	**-0.143***	**-0.188***	**-0.216***	**-0.138***	-0.042	-0.149	-0.180	-0.172	**-0.363***	**-0.234***	**-0.157***	**-0.174***
			(0.035)	(0.035)	(0.037)	(0.062)	(0.065)	(0.035)	(0.040)	(0.062)	(0.068)	(0.061)	(0.034)	(0.035)	(0.040)	(0.037)
		p=	<0.001	<0.001	<0.001	0.002	0.001	<0.001	0.296	0.017	0.008	0.005	<0.001	<0.001	<0.001	<0.001
Educational Attainment	*(ref. Less than 9th Grade)*															
	9-11th Grade (Incl. 12th Grade w/ No Diploma)	β	0.085	0.050	0.166	-0.151	0.079	0.066	0.055	-0.133	-0.140	-0.165	0.031	0.085	0.040	0.023
			(0.068)	(0.069)	(0.073)	(0.066)	(0.069)	(0.055)	(0.077)	(0.067)	(0.072)	(0.065)	(0.066)	(0.068)	(0.077)	(0.072)
		p=	0.211	0.463	0.022	0.021	0.251	0.231	0.475	0.046	0.054	0.011	0.635	0.211	0.608	0.747
	High School Grad/GED or Equivalent	β	0.116	0.025	0.119	-0.100	0.102	0.099	0.070	-0.137	-0.072	-0.101	0.015	0.116	0.017	0.024
			(0.063)	(0.064)	(0.067)	(0.063)	(0.065)	(0.052)	(0.072)	(0.064)	(0.069)	(0.062)	(0.062)	(0.063)	(0.072)	(0.067)
		p=	0.066	0.701	0.077	0.109	0.119	0.059	0.328	0.032	0.297	0.102	0.802	0.066	0.809	0.726
	Some College or AA Degree	β	**0.186***	0.066	0.165	-0.151	0.100	0.127	0.124	**-0.162***	-0.148	-0.151	0.043	**0.186***	0.068	0.042
			(0.062)	(0.062)	(0.066)	(0.062)	(0.064)	(0.051)	(0.070)	(0.063)	(0.068)	(0.061)	(0.060)	(0.062)	(0.070)	(0.066)
		p=	0.003	0.288	0.012	0.014	0.122	0.013	0.077	0.01	0.03	0.013	0.477	0.003	0.333	0.525
	College Graduate or Above	β	**0.218***	0.068	**0.219***	-0.035	0.119	**0.160***	0.127	-0.077	0.005	-0.053	0.049	**0.218***	0.063	0.054
			(0.065)	(0.066)	(0.069)	(0.067)	(0.071)	(0.055)	(0.074)	(0.068)	(0.074)	(0.067)	(0.063)	(0.065)	(0.074)	(0.069)
		p=	0.001	0.298	0.002	0.605	0.092	0.003	0.086	0.259	0.948	0.422	0.437	0.001	0.395	0.431
Family Poverty Income Ratio		β	**0.041***	**0.027***	**0.027***	**0.035***	0.024	**0.032***	0.019	0.029	**0.033***	**0.035***	0.020	**0.041***	**0.029***	0.019
			(0.008)	(0.009)	(0.009)	(0.011)	(0.011)	(0.008)	(0.010)	(0.011)	(0.012)	(0.010)	(0.008)	(0.008)	(0.010)	(0.009)
		p=	<0.001	0.002	0.003	0.001	0.03	<0.001	0.049	0.007	0.004	0.001	0.014	<0.001	0.003	0.037
Smoking Status	*(ref. Non-Smokers)*															
	Former Smoker	β	0.049	0.092	0.052	-0.088	-0.008	0.038	0.031	-0.095	-0.100	-0.086	**0.128***	0.049	0.088	0.066
			(0.042)	(0.043)	(0.044)	(0.052)	(0.055)	(0.039)	(0.048)	(0.053)	(0.057)	(0.051)	(0.041)	(0.042)	(0.048)	(0.045)
		p=	0.245	0.03	0.239	0.091	0.89	0.326	0.518	0.071	0.081	0.093	0.002	0.245	0.066	0.143
	Current Smoker	β	**0.138***	**0.140***	0.105	-0.053	-0.005	0.035	-0.049	-0.048	-0.082	-0.036	**0.193***	**0.138***	0.057	0.085
			(0.044)	(0.044)	(0.046)	(0.053)	(0.055)	(0.040)	(0.050)	(0.054)	(0.059)	(0.053)	(0.042)	(0.044)	(0.050)	(0.047)
		p=	0.002	0.001	0.023	0.325	0.925	0.384	0.324	0.37	0.161	0.494	<0.001	0.002	0.249	0.068
	Heavy Smoker	β	0.076	0.131	0.062	**-0.156***	0.015	0.079	0.019	-0.090	**-0.195***	-0.143	**0.186***	0.076	0.057	0.144
			(0.049)	(0.050)	(0.052)	(0.052)	(0.056)	(0.042)	(0.056)	(0.052)	(0.057)	(0.051)	(0.047)	(0.049)	(0.056)	(0.053)
		p=	0.121	0.008	0.231	0.003	0.788	0.062	0.735	0.086	0.001	0.005	<0.001	0.121	0.31	0.006
# Weekly Drinks		β	**0.009***	0.006	0.007	0.005	0.006	0.006	0.002	0.002	0.008	0.004	**0.009***	**0.009***	0.002	0.005
			(0.003)	(0.003)	(0.003)	(0.004)	(0.004)	(0.003)	(0.003)	(0.004)	(0.004)	(0.004)	(0.003)	(0.003)	(0.003)	(0.003)
		p=	0.002	0.032	0.028	0.182	0.121	0.032	0.598	0.505	0.057	0.245	0.001	0.002	0.539	0.088
Sedentary Hours/Day		β	-0.006	-0.010	-0.009	-0.008	0.002	-0.001	-0.009	-0.008	-0.012	-0.006	**-0.010***	-0.006	-0.009	-0.009
			(0.004)	(0.004)	(0.004)	(0.005)	(0.005)	(0.003)	(0.004)	(0.005)	(0.005)	(0.005)	(0.003)	(0.004)	(0.004)	(0.004)
		p=	0.095	0.005	0.02	0.067	0.695	0.8	0.022	0.109	0.02	0.171	0.003	0.095	0.031	0.014

Standard errors in parentheses. ***indicates significance (p≤0.004)**

Table 14. BMD and Covariate Associations by Anatomical Region. Men Only Subgroup

Anatomical Region		Weight-Bearing	Non-WeightBearing	Total BMD	Total Femur	Total Spine	Lumbar Spine	Thoracic Spine	Femoral Neck	Trochanter	Intertrochanter	Avg Arm	Avg Leg	Avg Rib	Pelvis
Men Only		3,479	3,530	3,408	2,742	2,256	5,840	3,674	2,742	2,742	2,742	3,603	3,479	3,674	3,674
BMI (kg/m^2)	β	**0.028***	**0.024***	**0.022***	**0.069***	**0.044***	**0.017***	**0.024***	**0.064***	**0.065***	**0.065***	**0.032***	**0.039***	**0.025***	**0.040***
		(0.002)	(0.002)	(0.003)	-0.003	(0.003)	(0.002)	(0.003)	(0.003)	(0.003)	(0.003)	(0.002)	(0.002)	(0.003)	(0.003)
	p=	<0.001	<0.001	<0.001	<0.001	<0.001	0.004	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Racialized G *(ref. Non-Hispanic White)*															
Non-Hispanic Black	β	**0.395***	**0.412***	**0.464***	**0.457***	**0.298***	**0.452***	**0.448***	**0.555***	**0.336***	**0.450***	**0.237***	**0.395***	**0.594***	**0.408***
		(0.028)	(0.028)	(0.030)	(0.039)	(0.037)	(0.026)	(0.030)	(0.040)	(0.043)	(0.037)	(0.026)	(0.028)	(0.032)	(0.030)
	p=	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Mexican-American	β	**-0.143***	**-0.137***	**-0.120***	-0.011	**-0.159***	**-0.138***	0.022	-0.001	**-0.161***	0.024	**-0.181***	**-0.143***	-0.064	-0.046
		(0.034)	(0.034)	(0.036)	(0.045)	(0.042)	(0.031)	(0.036)	(0.046)	(0.049)	(0.043)	(0.032)	(0.034)	(0.039)	(0.037)
	p=	<0.001	<0.001	0.001	0.802	<0.001	<0.001	0.545	0.98	0.001	0.571	<0.001	<0.001	0.105	0.221
Non-Hispanic Other	β	-0.099	**-0.118***	-0.067	0.089	-0.052	-0.047	0.021	0.115	0.031	0.116	**-0.171***	-0.099	-0.029	-0.047
		(0.039)	(0.038)	(0.040)	(0.051)	(0.050)	(0.035)	(0.041)	(0.053)	(0.056)	(0.049)	(0.035)	(0.039)	(0.044)	(0.042)
	p=	0.01	0.002	0.097	0.08	0.291	0.186	0.61	0.03	0.584	0.019	<0.001	0.01	0.509	0.26
Other Incl. Multi-Racial	β	**-0.108***	**-0.186***	**-0.096***	-0.055	-0.111	-0.099	0.023	-0.030	-0.127	-0.022	**-0.223***	**-0.108***	**-0.111***	-0.075
		(0.029)	(0.029)	(0.031)	(0.059)	(0.059)	(0.030)	(0.031)	(0.061)	(0.065)	(0.057)	(0.027)	(0.029)	(0.034)	(0.032)
	p=	<0.001	<0.001	0.002	0.351	0.058	0.001	0.465	0.63	0.051	0.703	<0.001	<0.001	0.001	0.018
Educational Attainment *(ref. Less than 9th Grade)*															
9-11th Grade (Incl. 12th Grade w/ No Diploma)	β	0.075	0.118	0.129	-0.060	0.095	**0.164***	0.121	-0.074	-0.035	-0.065	0.060	0.075	0.154	0.103
		(0.053)	(0.053)	(0.056)	(0.059)	(0.057)	(0.045)	(0.056)	(0.061)	(0.065)	(0.057)	(0.049)	(0.053)	(0.061)	(0.058)
	p=	0.159	0.025	0.021	0.313	0.097	<0.001	0.031	0.231	0.587	0.257	0.22	0.159	0.011	0.075
High School Grad/GED or Equivalent	β	0.050	0.057	0.089	-0.041	0.113	**0.148***	0.089	-0.068	0.007	-0.055	0.031	0.050	0.071	0.078
		(0.051)	(0.050)	(0.053)	(0.057)	(0.055)	(0.043)	(0.054)	(0.059)	(0.063)	(0.055)	(0.047)	(0.051)	(0.058)	(0.055)
	p=	0.323	0.257	0.094	0.47	0.042	0.001	0.096	0.249	0.909	0.32	0.512	0.323	0.222	0.158
Some College or AA Degree	β	0.088	0.063	0.099	-0.036	0.134	**0.183***	0.098	-0.076	-0.024	-0.030	0.005	0.088	0.112	0.117
		(0.051)	(0.051)	(0.053)	(0.059)	(0.057)	(0.044)	(0.054)	(0.061)	(0.065)	(0.057)	(0.047)	(0.051)	(0.058)	(0.055)
	p=	0.085	0.215	0.063	0.545	0.019	<0.001	0.068	0.215	0.707	0.6	0.922	0.085	0.054	0.035
College Graduate or Above	β	0.148	0.007	0.130	0.022	0.140	**0.168***	0.079	-0.005	0.010	0.027	-0.040	0.148	0.045	0.143
		(0.054)	(0.054)	(0.057)	(0.064)	(0.062)	(0.047)	(0.057)	(0.066)	(0.070)	(0.062)	(0.050)	(0.054)	(0.062)	(0.059)
	p=	0.006	0.893	0.023	0.733	0.024	<0.001	0.168	0.944	0.892	0.657	0.428	0.006	0.468	0.015
Family Poverty Income Ratio	β	**0.027***	**0.022***	**0.025***	0.019	0.015	0.017	0.012	0.006	0.025	0.017	**0.025***	**0.027***	0.018	**0.024***
		(0.007)	(0.007)	(0.008)	(0.010)	(0.010)	(0.007)	(0.008)	(0.010)	(0.011)	(0.010)	(0.007)	(0.007)	(0.008)	(0.008)
	p=	<0.001	0.002	0.001	0.052	0.109	0.012	0.12	0.536	0.023	0.074	<0.001	<0.001	0.027	0.003
Smoking Sta *(ref. Non-Smokers)*															
Former Smoker	β	-0.016	-0.013	-0.027	-0.117	-0.106	**-0.091***	-0.011	-0.044	**-0.160***	**-0.118***	0.008	-0.016	-0.034	-0.054
		(0.030)	(0.030)	(0.032)	(0.043)	(0.041)	(0.028)	(0.032)	(0.044)	(0.047)	(0.041)	(0.027)	(0.030)	(0.034)	(0.033)
	p=	0.604	0.663	0.391	0.006	0.011	0.001	0.73	0.322	0.001	0.004	0.769	0.604	0.322	0.094
Current Smoker	β	-0.022	0.038	-0.031	**-0.129***	-0.073	-0.073	-0.027	-0.052	**-0.189***	-0.112	0.055	-0.022	0.017	-0.042
		(0.032)	(0.031)	(0.033)	(0.045)	(0.043)	(0.029)	(0.033)	(0.047)	(0.050)	(0.044)	(0.029)	(0.032)	(0.036)	(0.034)
	p=	0.48	0.225	0.348	0.004	0.089	0.013	0.413	0.266	<0.001	0.01	0.057	0.48	0.631	0.221
Heavy Smoker	β	-0.009	0.039	-0.003	**-0.161***	-0.063	-0.069	-0.059	-0.113	**-0.209***	**-0.144***	**0.092***	-0.009	-0.021	-0.037
		(0.034)	(0.034)	(0.036)	(0.042)	(0.041)	(0.030)	(0.036)	(0.044)	(0.047)	(0.041)	(0.031)	(0.034)	(0.039)	(0.037)
	p=	0.793	0.247	0.929	<0.001	0.122	0.022	0.102	0.01	<0.001	<0.001	0.003	0.793	0.578	0.308
# Weekly Drinks	β	0.003	0.004	0.003	**0.007***	**0.005***	**0.005***	0.000	**0.007***	**0.008***	**0.006***	**0.004***	0.003	0.002	0.002
		(0.001)	(0.001)	(0.001)	(0.002)	(0.002)	(0.001)	(0.001)	(0.002)	(0.002)	(0.002)	(0.001)	(0.001)	(0.001)	(0.001)
	p=	0.02	0.007	0.046	<0.001	0.003	<0.001	0.816	<0.001	<0.001	0.001	0.001	0.02	0.09	0.113
Sedentary Hours/Day	β	-0.004	**-0.013***	-0.006	-0.005	-0.005	-0.006	-0.006	-0.006	-0.006	-0.005	**-0.013***	-0.004	-0.010	-0.004
		(0.003)	(0.003)	(0.003)	(0.004)	(0.004)	(0.003)	(0.003)	(0.005)	(0.005)	(0.004)	(0.003)	(0.003)	(0.004)	(0.003)
	p=	0.224	<0.001	0.095	0.223	0.236	0.048	0.088	0.17	0.239	0.237	<0.001	0.224	0.006	0.249

Standard errors in parentheses. ***indicates significance (p≤0.004)**