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The effects of orthopedic pathologies on the prevalence of hip osteoarthritis

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THE EFFECTS OF ORTHOPEDIC PATHOLOGIES ON THE PREVALENCE OF HIP OSTEOARTHRITIS

by

AUBRIE M. SANCHEZ

B.A., Boston University, 2014
M.P.H., Northeastern University, 2017

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Approved by

First Reader ____________________

Sean D. Tallman, Ph.D.
Assistant Professor of Anatomy & Neurobiology

Second Reader ____________________

Allysha Powanda Winburn, Ph.D.
Assistant Professor of Anthropology
University of West Florida, College of Arts, Social Sciences & Humanities

Third Reader ____________________

Joshua Stefanik, Ph.D.
Assistant Professor of Physical Therapy, Movement, & Rehabilitation Sciences
Northeastern University, Bouvé College of Health Sciences

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AUBRIE M. SANCHEZ

ABSTRACT

Osteoarthritis (OA) is a degenerative joint disease that is a leading cause of disability among aging adults. In the U.S., many individuals living with total hip arthroplasties attribute OA as the cause. Because the majority of anthropological OA research excludes pathological individuals (i.e., individuals with systemic disease, traumatic injuries, or arthroplasties), little is known about how prostheses and pathologies impact OA. This project adds to the research surrounding OA by investigating its relationship with age, disease, and prostheses.

The proximal femora of 186 African- and European-American individuals (21-95 years old) from the Edmonds Orthopedic Pathology Collection (National Museum of Health and Medicine; Armed Forces Institute of Pathology) were analyzed. These individuals were grouped into three cohorts: non-disease; disease; and previous injury/prosthesis. Jurmain's (1990) method was used to score OA, using an ordinal four-point scale to categorize OA changes as: none/slight; moderate; severe; and ankylosis.

Results show that osteoarthritic hip changes are positively correlated with age and presence of a prosthesis, and that systemic diseases, such as cancer, increase the likelihood of OA in an individual. Results from Chi-square tests, exploratory data analysis, and ordinal logistic regression show that there is a statistically significant relationship ($p<0.000$) between degree of OA, age, recorded disease, and evidence of previous injury or prostheses. In contrast with the expectation that different populations would exhibit different patterns of OA, no sex or ancestry effects are observed. These results will help researchers better understand the etiology and contemporary risk factors of OA, as well as contribute data to OA research on an underrepresented sample.

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LIST OF ABBREVIATIONS

AFIP	Armed Forces Institute of Pathology
BMD	Bone Mineral Density
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
EDA	Exploratory Data Analysis
MRI	Magnetic Resonance Imaging
NMHM	National Museum of Health and Medicine
OA	Osteoarthritis
UTK	University of Tennessee, Knoxville

INTRODUCTION

The current research explores the relationships between orthopedic pathologies of the proximal femur (i.e., implantation of intertrochanteric fracture fixation devices and surgical pins or total hip arthroplasties), disease (i.e., metastatic cancer), and the expression of osteoarthritis (OA) of the hip joint, and investigates the effects of age on hip OA. Osteoarthritis is a degenerative joint disease estimated to be one of the leading causes of disability in the U.S. (Racine, 2015) and the fourth leading cause of disability worldwide (Fransen et al., 2011; Zampetti et al., 2016). In the U.S., over 2.5 million individuals live with total hip arthroplasties (Kremers et al., 2015), of which 70% attribute OA as the cause (AJRR, 2016). Much previous anthropological research has excluded pathological individuals from OA analyses, which is not reflective of modern populations. If OA research is expected to contribute to more fully understanding the progression and etiology of the disease, pathological individuals must be included in further analyses. It is estimated that by the year 2020, nearly 20% of the U.S. population, approximately 60 million individuals, will be diagnosed with a musculoskeletal disease (Lawrence et al., 1998). Thus, the inclusion of modern pathological individuals in research is paramount to increasing the understanding of potential risk factors for OA. The National Institutes of Health's Genetic and Rare Diseases Information Center lists over 650 musculoskeletal diseases, which include, but are not limited to: fracture; dysplasia; rickets; arthritis; and gout. Since OA generally does not occur in isolation and may, in fact, be affected by disease or trauma, it is important to understand the relationship between osteoarthritic changes and other pathological conditions. At present, research has neglected to examine the intersection of OA and disease, leading to an incomplete view of variation in the expression of OA and its multifactorial etiology. Excluding individuals with known pathologies from current OA research in anthropology limits the relevance of the results for nearly one fifth of the U.S. population. With the assistance of the Edmonds Orthopedic Pathology Collection from the National Museum of Health and Medicine (NMHM) located at the Armed Forces Institute of Pathology (AFIP) in Silver Spring, MD, this research will begin to fill that gap.

Osteoarthritis is a complex disease whose etiology remains only partially understood. Early research accepted OA as a disease that primarily affects the articular cartilage within synovial joints (Solomon, 1976); however, the current understanding of OA has shifted to involve both the cartilage via chondrocytes and the hard tissue element via subchondral bone as a disease of the entire joint organ rather than just an isolated disease of articular cartilage (Felson, 2004; Felson and Neogi, 2004; Brandt et al., 2006). Synovial joints, or diarthroses, represent relatively mobile articulations of skeletal elements (Neu et al., 2008). The articular ends of each bone, and the joint space between them, are surrounded by a capsule which contains hyaline articular cartilage and synovial fluid. Ligaments and muscles surround the joint capsule and assist with both movement and stability of the joint. The hip joint is comprised of the acetabulum of the os coxa and the femoral head, and it allows for movement of the proximal lower limb (thigh). There are three ligaments and 27 muscles that act on the hip joint and allow for human bipedal locomotion (Sariali et al., 2008). Over time, multiple factors such as disease, changes in hip alignment, and developmental morphology can contribute to the degeneration of articular cartilage (Hamerman, 1989) and serve as biomechanical risk factors for the development of OA. The etiology of OA is different from other types of arthritis, as its progression is degenerative rather than inflammatory (Felson, 2004; Lowman, 1955). Rheumatoid arthritis is an erosive inflammatory disease that can be differentiated from OA; rheumatoid arthritis primarily destroys bone, while OA is reactive and is characterized by both osteoblastic and osteoclastic activity accompanied with remodeling (Findlay and Atkins, 2014; Kirchengast, 2015; Maruotti et al., 2017; Rothschild et al., 1990). Synovial joints of the lower limb, in particular, provide a unique perspective for observing OA in the human skeleton due to their involvement in locomotion. There are six different types of synovial joints in the human body: pivot, hinge, saddle, plane, condyloid, and ball-and-socket; and observing the macroscopic skeletal alterations in bone associated with cartilage destruction, subchondral bone sclerosis, and synovial tissue metabolism within these joints may help reveal the risk factors for OA (Felson, 2004; Garnero et al., 2001). Clinical and anthropological investigations into the etiology of OA have shifted from a focus on activity as the primary risk factor for the disease (Felson and Zhang, 1998; Larsen 1982; Larsen, 1997) to examining the role of obesity as a contributing risk factor, as well (Coggon et al., 2001; Felson, 1988; Felson et al., 2000; Fransen, 2011; Mandl, 2007; Weiss and Jurmain, 2007). Additionally, researchers are beginning to investigate the effects of how these risk factors may interact with each other and, thus, how they affect the development and progression of OA.

Assessing OA in Clinical and Anthropological Contexts

The goal of clinical assessments of OA is to ensure the highest quality of life for an individual living with disease or traumatic injury. Thus, clinical epidemiologists focus their research on antemortem analyses of disease and trauma patterns, treatments, pain management, and intervention outcomes (Roger 2011; Zhang and Niu 2016). Gait analysis is a major component of clinical diagnosis and non-surgical treatment of OA. Radiographs and gait pattern analysis both before and after intervention are crucial in providing minimally invasive techniques to assess disease progression, and can provide kinetic and kinematic biomechanical data on OA (Aminian et al., 2004). Beaulieu et al. (2010) demonstrate that after an individual undergoes a total hip arthroplasty, gait patterns do not return to normal. They investigated the biomechanical (kinetic and kinematic) effects of a total hip arthroplasty on both the affected leg and the non-operative leg at the hip, knee and ankle. Deviations from normal gait patterns were most prevalent in the affected hip joints, and individuals who underwent surgery displayed lower peak angles in flexion, extension, adduction, external rotation and sagittal-plane range of motion compared to the control group (Beaulieu et al., 2010). With this altered gait cycle in mind, it is important to consider the potential effects of prostheses on the anatomy of the hip and how this may affect the prevalence of osteoarthritis for individuals with hip prostheses.

The pathogenesis of OA can be influenced by several factors. Research surrounding OA and its progression from a clinical context have incorporated considerations such as bone mineral density (BMD) (Barbour et al., 2015; Chan et al., 2014; Dequeker et al., 1995; Lee et al., 2013) and traumatic injury (Anderson et al., 2011; Chammas, 2014; Coughlin and Kennedy, 2016; Lieberthal et al., 2015; Rodeo et al., 2017; Thonar et al., 1995; Wellsandt et al., 2017). There is limited agreement in the literature regarding how increased BMD can affect the expression and progression of OA. Barbour et al. (2015) used data from The Johnston County Osteoarthritis Project and found that high levels of BMD may increase one's risk for OA. Dequeker et al. (1995) found that osteoarthritic joints display an increased BMD. The goal of their research was to investigate the mechanical properties of the underlying subchondral bone in osteoarthritic joints, and to examine whether or not these alterations affect an individual's propensity to develop progressive OA. Scrutiny should be applied in comparing clinical data to bioarchaeological or anthropological data as methods for detection and diagnosis of OA differ between the field, as cartilage degeneration and joint space narrowing are not visible in skeletal remains. Cartilage loss was found to be associated with BMD loss in a study on 127 subjects over a two-year period (Lee et al., 2013). Chan et al., (2014) examined data from the Dubbo Osteoporosis Epidemiology Study on BMD and its association with OA and fracture risk in both males and females. Their results showed that females with combined lower BMD and OA had an increased risk for fracture. Where traumatic injuries are involved, specifically fractures, individuals may be at an increased risk for developing OA, and these factors play an integral role in a physician's treatment plan. Inflammation after injury is the primary catalyst for OA after traumatic injury (Anderson et al., 2011; Kumar et al., 2019; Lieberthal et al., 2015). Increased inflammatory signaling in the affected area can also be altered by systemic factors, such as obesity, and aging (Lieberthal et al., 2015), which are also important factors to take into consideration in OA research stemming from osteological studies in bioarchaeology and anthropology. Clinical research on the relationship between OA and both BMD and traumatic injury is intricate, and requires further investigation in order to mitigate this disjuncture. The current research aims to bridge the gap between modern clinical medicine and paleopathological analyses.

Clinical epidemiologists and bioarchaeologists categorize OA differently due to the different mechanisms in diagnosing and scoring the disease. In clinical settings, OA is primarily assessed primarily through radiographs showing diminished joint space, osteophytic growth, and subchondral sclerosis, or magnetic resonance imaging to show bone marrow lesions (Bijlsma et al., 2011; Calce et al., 2017; Felson et al., 1987) using the Kellgren-Lawrence ordinal grading system (Kellgren and Lawrence, 1957). However, it is not possible to diagnose OA in dry bone by examining for diminished joint space. A macroscopic approach to skeletal analysis outside of the context of clinical pain management is suggested because the presence of osteophytes or minor erosion in the joint are not visible radiographically (Jurmain and Kilgore, 1995). Additionally, visual scoring is more sensitive than clinical scoring, making diagnosis easier when presented with dry bone (Rogers and Dieppe, 1994).

In an attempt to bridge the gap between clinical and bioarchaeological studies on OA, Jurmain (1990) published an ordinal scoring method based on degree of severity of the disease. In this and other skeletal OA-analysis methods, the primary dry-bone features categorizing OA are lipping, porosity, osteophytes, and eburnation (Brennaman et al., 2017; Buikstra and Ubelaker, 1994; Jurmain, 1980; Jurmain, 1990; Waldron and Rogers, 1991). The presence of eburnation on the joint surface is considered best practice for diagnosing OA in skeletonized remains, as it is pathognomonic for OA (Brandt et al., 2009; Rogers et al., 2004; Waldron, 1993; Wallace et al., 2017). Although clinical research is of significant importance in diagnosing skeletal pathologies for both individuals and populations, it is also important to investigate the prevalence of those pathologies within an anthropological or bioarchaeological context in order to better understand the causes, disease progression, and possible risk factors associated with the disease. Additionally, pathology is of importance in forensic contexts, as pathologies can assist in the identification of unknown individuals if detailed antemortem records of the pathology exist in medical records.

Pathophysiology of OA

Osteoarthritis is an ancient disease, but little research has been conducted to catalog its epidemiology in modern populations within an anthropological or bioarchaeological context outside of frequency calculations (Jurmain and Kilgore, 1995). The pathophysiology of OA remains widely unknown; recent research acknowledges its multifactorial etiology (Brickley and Waldron, 1998; Calce et al., 2018a; Chan et al., 2014; Chen et al., 2017; Debono et al., 2004; Felson, 1996; Felson and Zhang, 1998; Manek et al., 2003; Spector and MacGregor, 2004), and this may be exacerbated by the fact that risk factors have changed and/or diversified over the past decades (e.g., life expectancy and obesity have increased, physical activity has decreased). Age is one of the primary influences in the likelihood of an individual to develop OA (Domett et al., 2017; Eng, 2016; Jurmain, 1980; Weiss and Jurmain, 2007; Winburn, 2017). Osteoarthritis is a degenerative joint disease that is pathological rather than physiological and primarily associated with age in nearly every joint (Jurmain, 1980), and recent anthropological research suggests it could be a powerful tool in skeletal age estimation. The three main methods of age estimation based on OA that exist assess the degree of OA in the vertebral column, shoulder, and hip. Age-at-death estimation methods based on the shoulder provide an alternative method for fragmentary remains, and those based on the acetabulum provide more narrow age ranges for older individuals.

Osteoarthritic changes of the vertebral column were identified as useful indicators of age by Stewart (1958) and Snodgrass (2004); however, Listi and Manhein (2012) argued that these methods are do not offer enough statistical power for narrow age ranges, and that these methods are only useful for broad age estimates. At a minimum, the documentation of general patterns of thoracic vertebral OA show general age-related patterns of osteophyte development that can be useful in establishing upper and lower limits for age-at-death estimation (Snodgrass 2004). Brennaman et al. (2017) explored the utility of shoulder OA as an age-at-death estimator, where individuals were categorized into eight age cohorts, ranging from 20 to 101 years, and scored based on the degree of lipping, porosity, osteophyte growth, and eburnation at the four joint surfaces of the shoulder (Brennaman et al., 2017). The authors developed this method, which resulted in an average of 74% accuracy at the left and right shoulders, to fill a gap in available aging techniques that may be applied to fragmentary remains (Brennaman et al., 2017). Rissech et al. (2006) developed a method of age estimation using age-related changes in the acetabulum and scored the individuals based on seven traits. As with any method, the work of Rissech et al. (2006) prompted validation studies and revisions (Calce, 2012; San-Millán et al., 2016). While San-Millán et al., (2016) agreed with Rissech et al.'s (2006) results, Calce (2012) found that the age ranges reported in the original study may be too narrow based on current knowledge of the progressive changes of the acetabulum. Additionally, Calce (2012) proposed a revision to the original method developed by Rissech et al., (2006), providing improved descriptions and the use of only three characteristics (those with the greatest statistical significance). The work of Winburn (2018) on a sample of 409 European-American individuals from the William M. Bass Donated Skeletal Collection (University of Tennessee, Knoxville) indicated strong positive correlations between acetabular changes and both OA and age. This suggests a degenerative etiology for the age-related changes of the acetabulum, i.e., they are linked with OA (Calce et al., 2018b). These changes were relatively resistant to the effects of obesity and physical activity within this population, suggesting that changes of the acetabulum are valid indicators of age. Thus, recent research indicates that OA changes can be useful for age estimation. However, if OA is influenced by musculoskeletal diseases and prostheses, then the use of OA as a general or more specific age indicator is problematic without further investigating the effects of orthopedic pathologies on the development and progression of OA.

Other factors, such as weight (Kulkarni et al., 2016; Thijssen et al., 2015), sex (Coggon et al., 2001; Felson, 1988; Felson and Zhang, 1998; McKean et al., 2007; Winburn, 2017), disease (Berenbaum, 2013; Lagier, 1985; Ramonda et al., 2012), and trauma (Chuckpaiwong et al., 2009; Coggon et al., 2001), may also influence the onset and severity of OA. High BMI and obesity specifically have been established as a critical risk factor for the development of OA. The increased risk factor for OA due to obesity is not simply attributed to excessive joint loading. Rather, the relationship between obesity and OA is much more nuanced and complicated than a "wear and tear" interpretation (Berenbaum, 2013; Peterson et al., 2010; Thijssen et al., 2015). Different ancestral populations may exhibit different patterns of the disease (Jurmain and Kilgore, 1995). Genetic factors contribute to nearly 60% of the risk factors for hip OA (Spector and MacGregor, 2004), which include obesity and collagen encoding genes, which play a key role in the production and maintenance of cartilage (Cimmino and Parodi, 2004).

Many bioarchaeologists continuously attribute the etiology of OA to behavior or physical activity (Agarwal 2012; Calce et al., 2018a; Domett et al., 2017). Several bioarchaeological studies analyzing a range of assemblages from the Bronze Age to the Iron Age, and of hunter-gatherers, agriculturalists, and pastoralists attribute activity and lifestyle to the development of skeletal pathologies (Bridges, 1991; Calce et al., 2018a; Debono et al., 2004; Eng, 2016; Jurmain and Kilgore, 1995; Knüsel, 1993; Larsen, 1982; Larsen, 1997; Molnar et al., 2011; Weiss and Jurmain, 2007; Winburn, 2018). These studies show that individuals within the same population often share similar patterns of OA within the same time period, and that the differences in patterns of the degenerative joint disease do not emerge unless marked differences in the functional stress of joint compartments are observed (Eng, 2016). However, much recent research challenges an activity-led etiology for OA by suggesting that activity may improve joint health rather than act as a catalyst for degenerative joint changes (Calce et al., 2018a,b; Domett et al., 2017; Hunter and Eckstein, 2009; Tak et al., 2005; Urquhart et al., 2011; Wallace et al., 2017; Winburn, 2017). A recent study by Wallace et al. (2017) challenges this traditional activity-OA paradigm by examining knee OA on the distal femur and proximal tibia through the identification of eburnation in three populations: prehistoric hunter-gatherers, early industrial individuals and post-industrial individuals. The authors briefly defined OA as joint degeneration due to biomechanical factors, but endeavored to determine the multiple etiologies of the disease. The authors analyzed a total of 2,576 skeletons, and they scored OA based on the presence or absence of eburnation on the joint surfaces. Since the prevalence of knee OA increases with age, it is logical to presume that the increasing life expectancy in U.S. populations (post-industrialists) plays a primary role in the current, increasing OA trends. With obesity being a recent epidemic in the U.S. (Ogden et al., 2011), exponentially increasing since the 1970s (Mitchell et al., 2011), the body mass index (BMI) can also be considered a risk factor for developing knee osteoarthritis. An individual with heightened BMI, calculated using a ratio of their mass and height, experiences an increased biomechanical loading on the affected weight-bearing joint (Weiss and Jurmain, 2007). This increased load can lead to both cartilage destruction and osteophytic lesions (Zhou et al., 2014), two of the main clinical indicators of OA.

Wallace et al. (2017) found that the prevalence of knee OA increased in the post-industrial population compared to the early industrial and prehistoric populations. Both age and body mass were contributors to the increased prevalence of knee OA within these populations, as the variables were found to be positively statistically correlated. However, the increased life expectancy and increased BMI were not enough to explain the increasing prevalence of the disease at its current rate. This holistic study can serve as a framework for future investigations of the multifactorial etiology of OA. However, its limitations include lack of study population diversity (focusing primarily on European-American individuals) and the potential underestimation of OA prevalence (ignoring skeletal changes such as subchondral porosity, lipping, and osteophytes, which are generally accepted in other anthropological studies (Brennaman et al., 2017; Buikstra and Ubelaker, 1994; Calce et al., 2017; Calce et al., 2018a; Jurmain, 1990; Zampetti et al., 2016). In order to gain a comprehensive knowledge on the etiology of OA, researchers should also investigate differences in the prevalence of knee osteoarthritis between the patellofemoral and tibiofemoral joint compartments, as location is an important consideration in the investigation of OA prevalence. Isolated tibiofemoral and patellofemoral joint OA or occurrence in both joint compartments has been shown to have differentiating clinical expressions in terms of clinical diagnosis and severity (Duncan et al., 2006; Stefanik, 2010; Szebenyi et al., 2006).

This study investigates the effects of orthopedic pathologies on the prevalence of hip OA in modern African- and European-American individuals from the Edmonds Orthopedic Pathology Collection at the National Museum of Health and Medicine

(NMHM) located at the Armed Forces Institute of Pathology (AFIP) in Silver Spring, Maryland. The first author observed the proximal femora of 186 individuals and diagnosed OA based on ordinal scores of appendicular OA (Jurmain, 1990). It was hypothesized that osteoarthritic changes of the hip are positively correlated with age and prosthesis implants compared to individuals lacking prostheses, and that the prevalence of OA is positively correlated with other systemic disease. The relationship between systemic diseases and osteoarthritis (OA) is an important consideration in modern human skeletal biology research as it investigates modern disease processes and the effects these common diseases may have on individuals. These effects may have many implications in multiple scientific fields, such as anatomy, anthropology, clinical epidemiology, orthopedic surgery, and biomechanics. For example, if OA is influenced by disease and prostheses, then osteoarthritic age indicators may be misleading, resulting in over-estimates. Additionally, understanding these effects can assist in bioarchaeological research, forensic identification in an anthropological context, as well as disease progression and mitigation in a clinical context.

MATERIALS AND METHODS

Skeletal Sample

The NMHM Edmonds Orthopedic Pathology Collection housed at the AFIP consists of approximately 365 individual adult elements, most notably proximal femora. These elements are pathological in that they contain: hip prostheses consisting of surgical plates, surgical pins, and total hip arthroplasties (Figures 1 and 2); intertrochanteric prostheses (Figure 3); antemortem fractures; bony alterations due to disease; and lesions attributed to metastatic carcinoma.

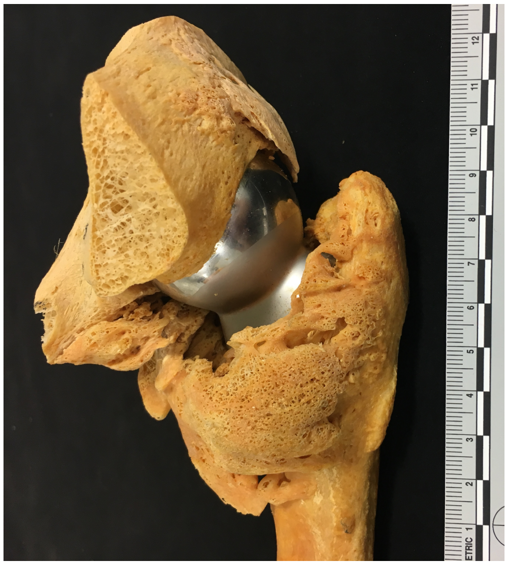


Figure 1. Example of proximal femur (posterior view) with total hip arthroplasty. Scale is in cm.

Figure 2. Example of proximal femur (lateral view) with surgical pins. Scale is in cm.

Figure 3. Examples of proximal femora (posterolateral views) with intertrochanteric prostheses. Scales are in cm.

The elements were curated by an orthopedic physician between 1958 and 1972, donated to the AFIP and relocated to the NMHM at its inception in 1989. For the purpose of this study, the first author examined the proximal femora of 186 individuals of European-American (n=144) and African-American (n=42) ancestry who were 21-95 years at the time of death (Figures 4-9). In total, 120 females and 66 males were observed. Associated autopsy records were available for most of the individuals, from which evidence of pathological conditions, diseases, and prostheses were recorded. Thus, the sample was divided into three cohorts: disease; non-disease; and previous injury/prosthesis. Of the 186 individuals in this sample, 93 were in the previous injury/prosthesis cohort, 24 in the non-disease cohort, and 69 in the disease cohort (Figures 4-9). Of the 69 individuals in the disease cohort, 49 were diagnosed with cancer (n = 29, breast; n=7, lung; n=4, prostate; n=9, other). Other diseases noted in antemortem records include, but are not limited to: Paget’s disease; osteomyelitis; gangrene; diabetes mellitus; and sickle cell anemia.

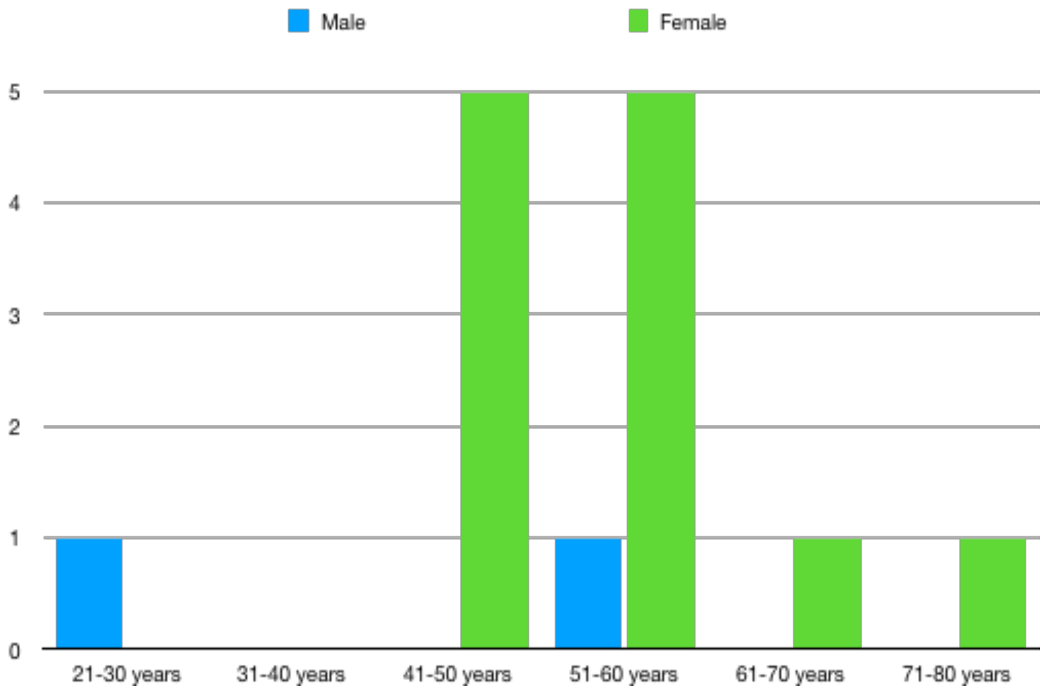


Figure 4. Histogram showing number of individuals by age-at-death for the African-American "Disease" cohort.

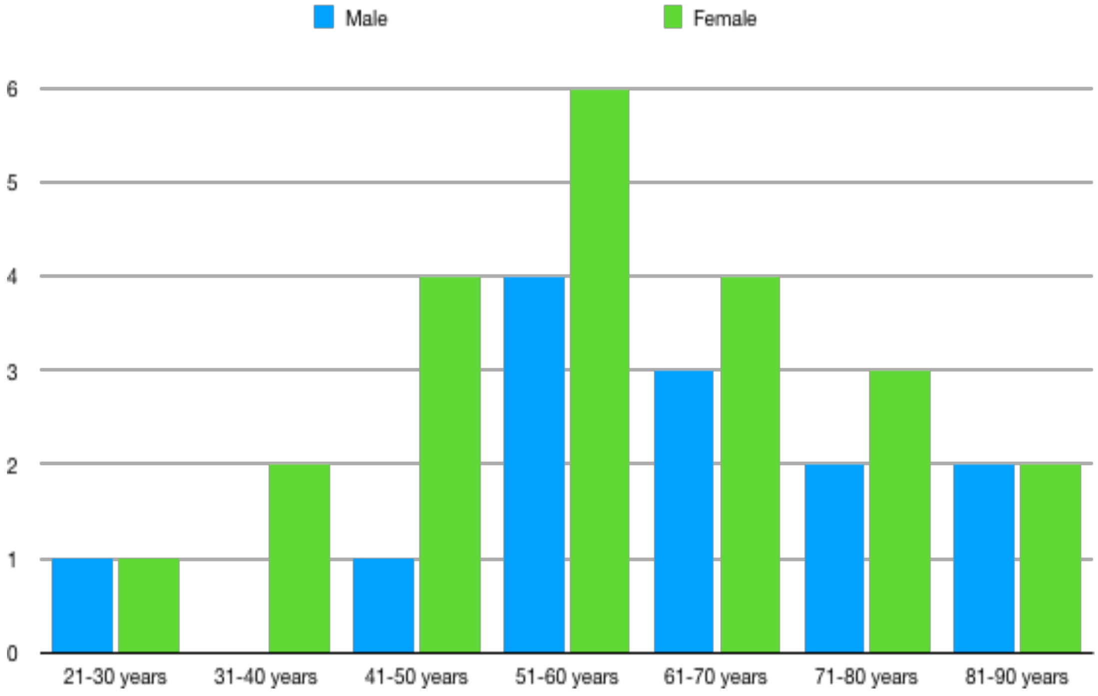


Figure 5. Histogram showing number of individuals by age-at-death for the European-American "Disease" cohort.

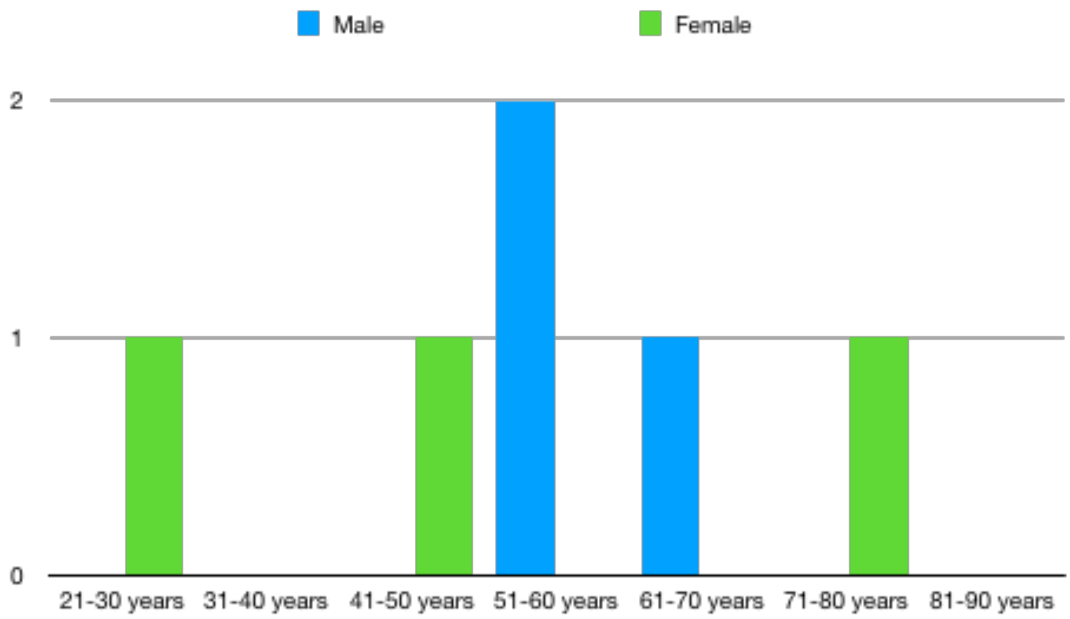


Figure 6. Histogram showing number of individuals by age-at-death for the African-American "Non-Diseased" cohort.

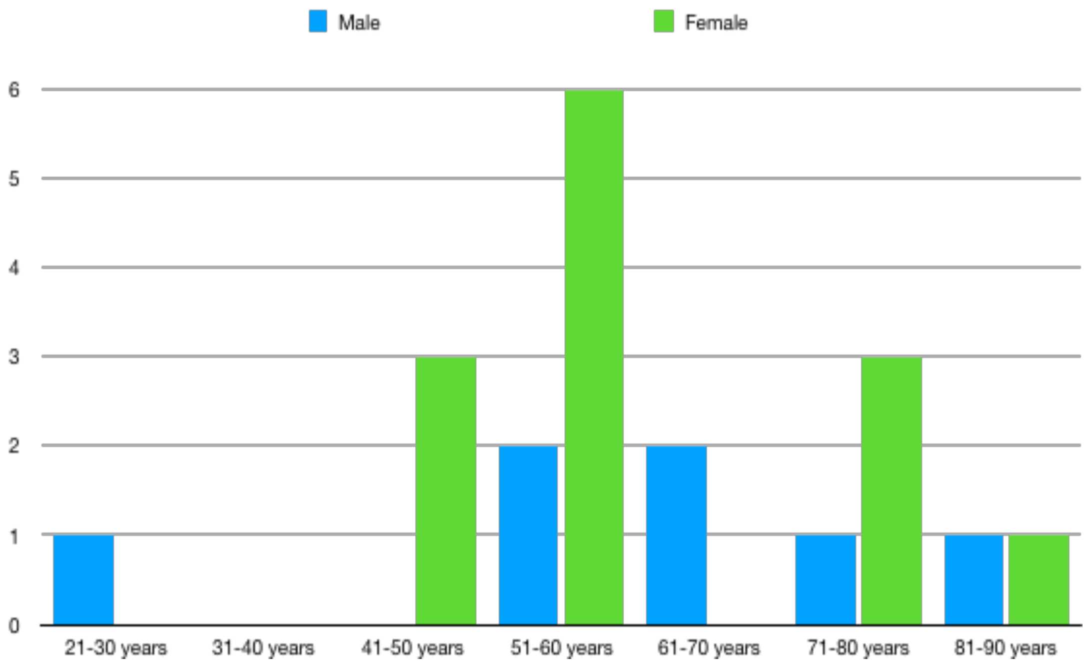


Figure 7. Histogram showing number of individuals by age-at-death for the European-American "Non-Diseased" cohort.

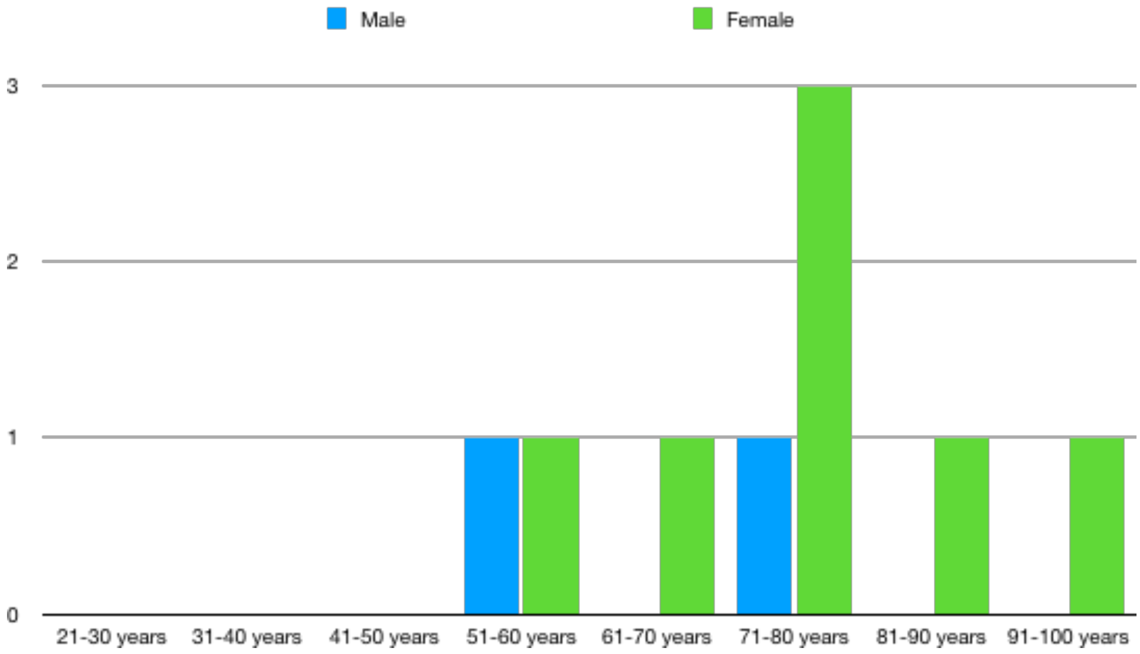


Figure 8. Histogram showing number of individuals by age-at-death for the African-American "Previous Injury/Prosthesis" cohort.

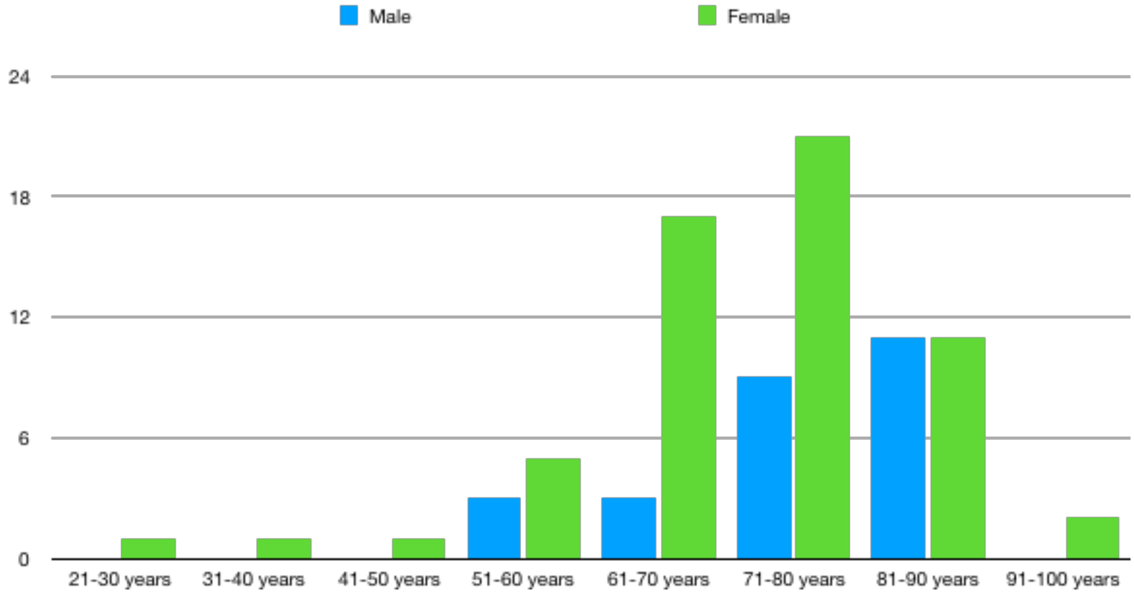


Figure 9. Histogram showing age-at-death cohorts for the European-American "Previous Injury/Prosthesis" cohort.

Methods

The presence and degree of OA were observed and scored on the proximal femur. Elements scored were selected from the collection by another anthropologist, so that the first author was blind to the demographic information at the time of data collection. The first author scored the elements following Jurmain (1990), using an ordinal scoring system with four categories: none/slight; moderate; severe; and ankyloses (Table 1; Figure 10).

Table 1. Osteoarthritis scoring system for severity (adapted from Jurmain [1990]).

Ordinal Score	Feature	Description of Feature
0	None/Slight	No joint surface changes
1	Moderate	Small osteophyte; and/or pitting over <10% of articular surface
2	Severe	Very large osteophyte; and/or pitting >10% of articular surface; or any evidence of eburnation
3	Ankylosis	Joint fusion

With a score of 0, the individual presents no, or slight, OA with no joint surface changes. A score of 1 indicates moderate OA changes at the joint surface as characterized by either isolated small osteophytes or small osteophytes in combination with pitting over less than 10% of the articular surface. Severe OA, a score of 2, is indicated by either isolated very large osteophytes or very large osteophytes in combination with pitting over more than 10% of the articular surface. Additionally, any evidence of eburnation on the joint surface will denote a score of 2. Ankylosis, or complete joint fusion, indicates a score of 3. A subset of 17 individuals studied were re-scored to examine intraobserver error, as well as scored by another professional anthropologist to examine interobserver error.

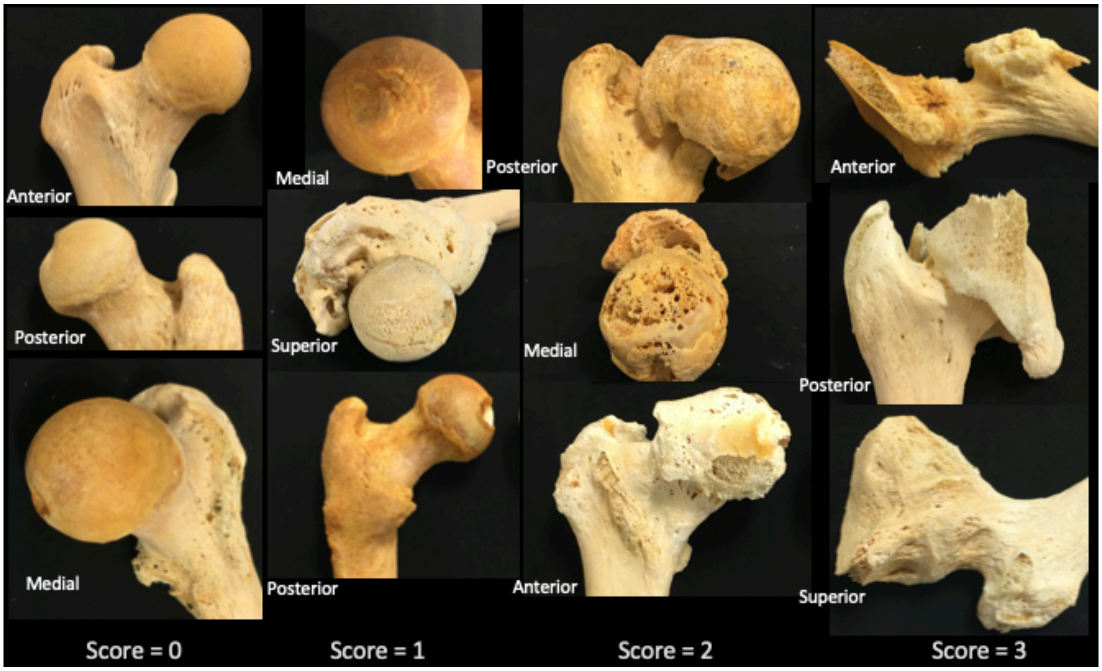


Figure 10. Visual representation of the ordinal scoring system of proximal femur OA.

Due to the ordinal data (i.e., lacking normality), nonparametric statistical analyses were conducted (Table 2), including: Chi-square; Spearman's rank correlation; exploratory data analysis (EDA); ordinal logistic regression; and Cohen's kappa. Chi-square tests were run as a test of independence to determine whether or not there was a relationship between the degree of OA and presence of previous injury, prostheses, or disease. Three Chi-square tests were run to test independence of assigned femur scores for only left femora, only right femora, and both left and right femora combined.

Table 2. Description of statistical tests conducted for the current research.

Statistical Test	Description
Spearman’s rank correlation	Detect variation in femur score between left and right femora within each individual (Field, 2009)
Chi-square	Test of independence (relationship between femur score and cohort) (Field, 2009)
Exploratory data analysis	Investigate group differences (average femur scores in different cohorts) (Field, 2009)
Ordinal logistic regression	Predict the probability of an individual having OA (Field, 2009)
Cohen’s kappa	Intra- and interobserver error (Landis and Koch, 1977)

Spearman’s rank order correlations were performed to test independence between left and right femur scores per individual. Exploratory data analysis was conducted in order to examine the distribution of femora in terms of their OA score, group (non-disease, disease, or previous injury/prosthesis), sex, and ancestry. Data were also subjected to an ordinal logistic regression to determine the effect of the orthopedic pathology and an individual’s age on the prevalence of OA within this sample. Both a binomial logistic regression and a multilevel binomial logistic regression were performed by combining assigned femur scores 1, 2, and 3. By combining these scores into one group, a direct comparison was possible between none/slight and moderate/severe/ankylosis individuals. Lastly, inter- and intraobserver error rates were calculated using Cohen’s kappa to account for the probability of agreement between researchers. In order to determine the agreement between researchers, Cohen’s kappa values were compared to Landis and Koch’s (1977) strength of agreement, which ranges in Cohen’s kappa values from -1 to 1. A Cohen’s kappa value of <0.00 represents poor agreement, between 0.00 and 0.20 represents slight agreement, between 0.21 and 0.40 represents fair agreement, between 0.41 and 0.60 represents moderate agreement, between 0.61 and 0.80 represents substantial agreement, and between 0.81 and 1.00 represents almost perfect agreement (Landis and Koch, 1977).

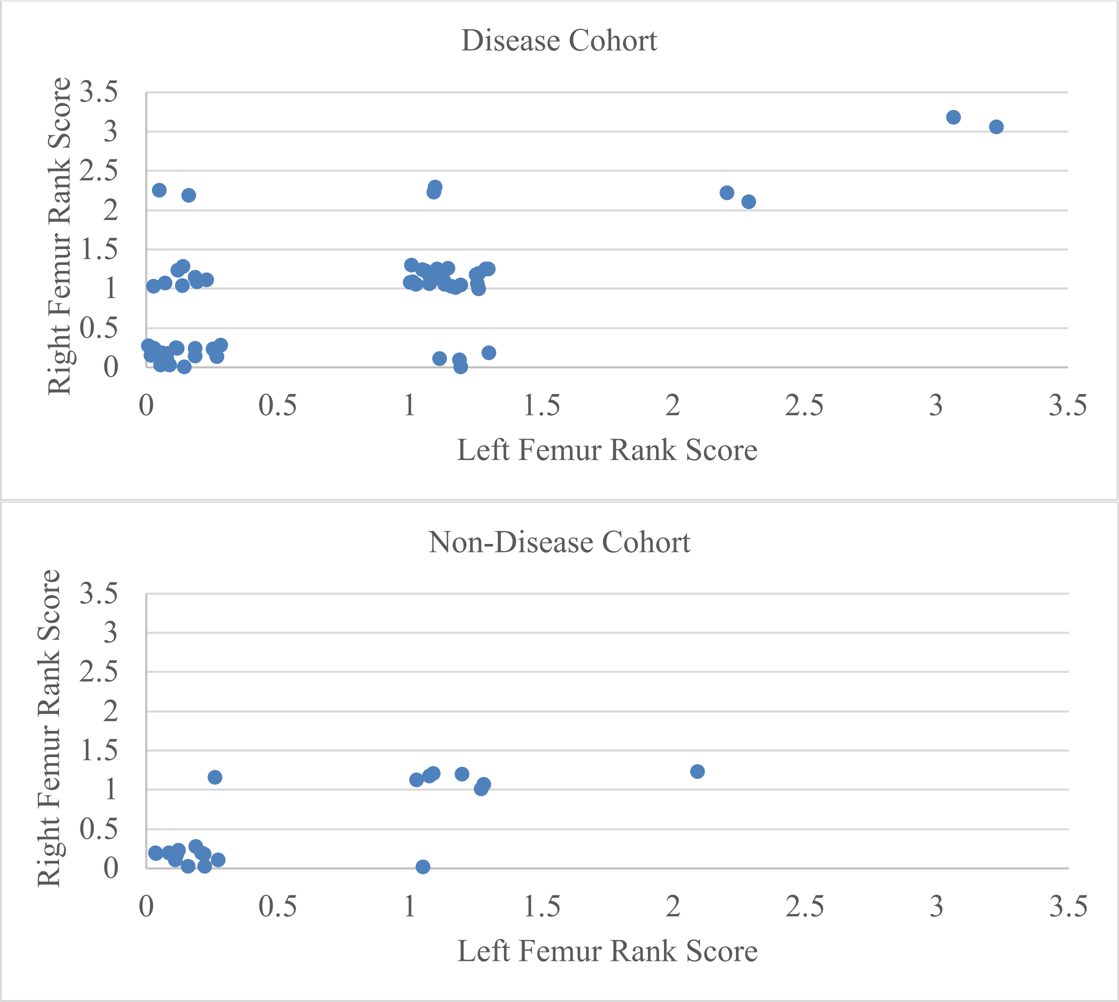
RESULTS

Results of the Chi-square tests on the three sample cohorts (disease, non-disease, and previous injury/prosthesis) show that there is a statistically significant relationship (p<0.000) between degree of OA, recorded disease, and evidence of previous injury or prostheses (Table 3).

Table 3. Results of the Chi-square analysis for all individuals (both left and right femora), showing a significant relationship between degree of OA and presence of disease or previous injury/prosthesis.

	OA Scores			
	0	**1**	**2 and 3**	**Total**
Non-Disease	26	15	1	42
Disease	51	61	8	120
Previous Injury/Prosthesis	42	82	32	156
Total	119	158	41	318
EXPECTED COUNTS				
Non-Disease	15.7169811320755	20.8679245283019	5.41509433962264	42
Disease	44.9056603773585	59.622641509434	15.4716981132075	120
Previous Injury/Prosthesis	58.377358490566	77.5094339622642	20.1132075471698	156
Total	119	158	41	318
PEARSON RESIDUALS				
Non-Disease	6.72778545380416	1.65002217748814	3.59976332916968	6.72778545380416
Disease	0.827088948787061	0.0318187246238357	3.60828347906121	0.827088948787061
Previous Injury/Prosthesis	4.59455306070179	0.26016424460003	7.02502743459946	4.59455306070179
	28.3245068528753	Chi-squared		
	6	df		
	0.0000816195138805381	p-value		

Scatter plots of the Spearman's rank order correlations assessing individual variation between left and right femoral OA scores indicate that both the disease and non-disease cohorts show significant associations in their left and right scores (Figure 11). However, the left and right OA scores for the previous injury/prosthesis cohort show no obvious relationship.



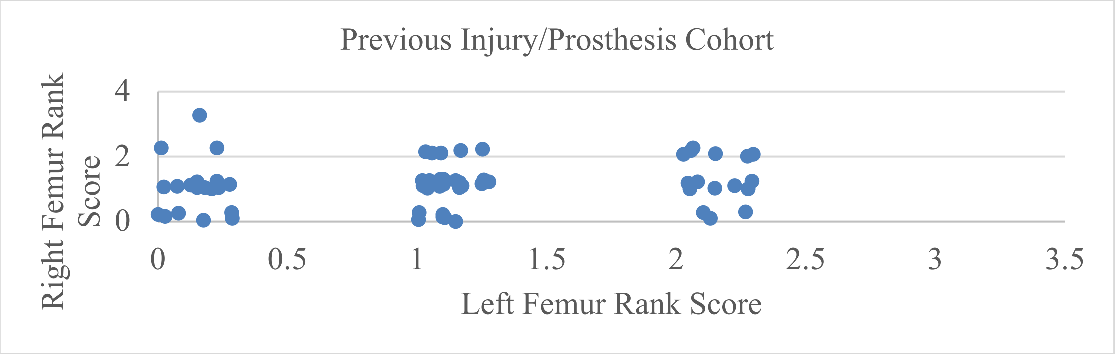


Figure 11. Scatter plots showing results of Spearman's rank correlations (blue dots are rank correlation sums).

Exploratory data analysis examined the distribution of femora according to: OA score; age; presence of previous injury, prostheses, or disease; sex; and ancestry. An age distribution plot revealed that most femora for individuals within the previous injury cohort were older than 55 years (Figure 12).

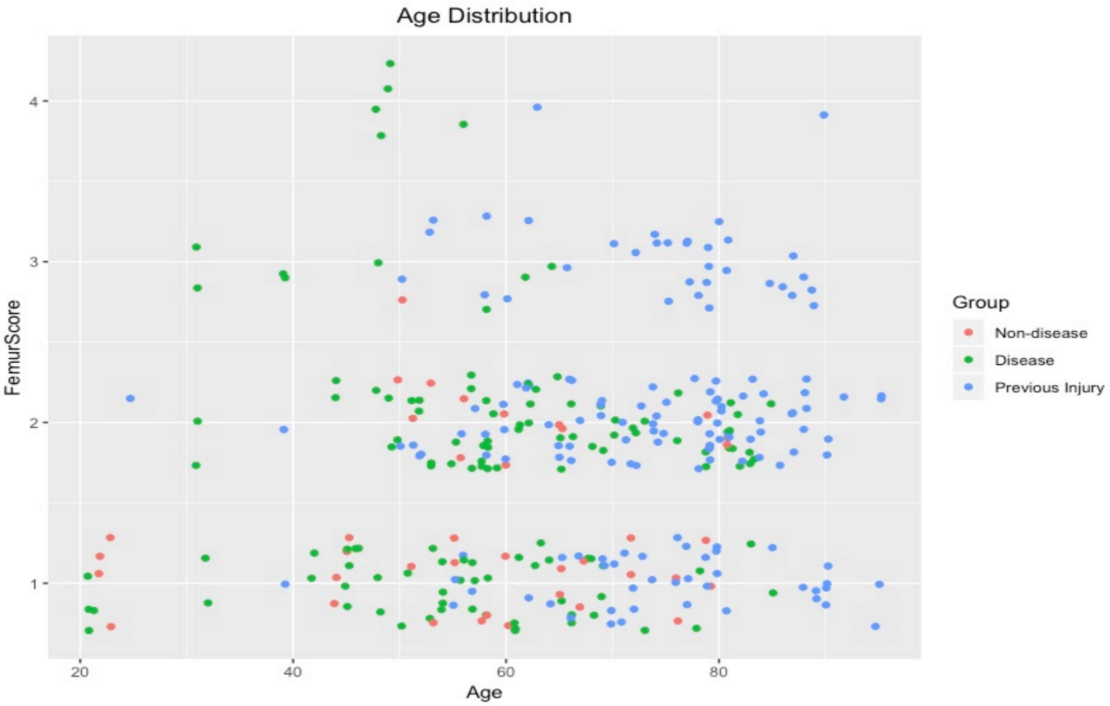


Figure 12. Age distribution plot depicting the age of each individual plotted against their average femur score for both femora by cohort.

Further, femora scored as severe and ankylosed (2) were mostly older individuals. Violin plots were created to examine differences in femur scores by sex (Figure 13), ancestry (Figure 14), and disease cohort (Figure 15). No differences in femur score for sex or ancestry were seen; however, there is a clear difference in the average femur scores among cohorts (red dots in Figure 15).

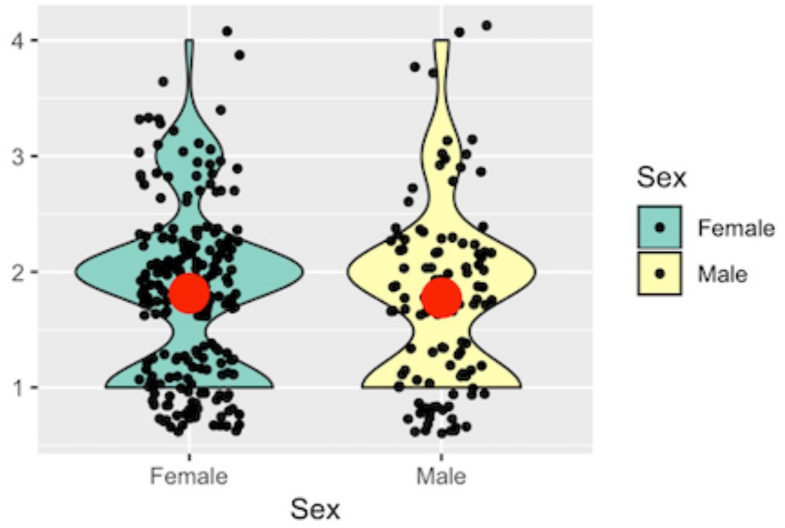


Figure 13. Violin plots illustrating no significant differences in the average femur score (red dots) by sex.

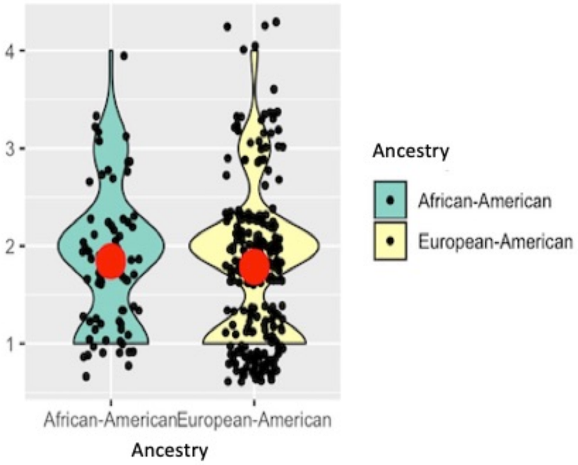


Figure 14. Violin plots illustrating no significant differences in the average femur score (red dots) by ancestry.

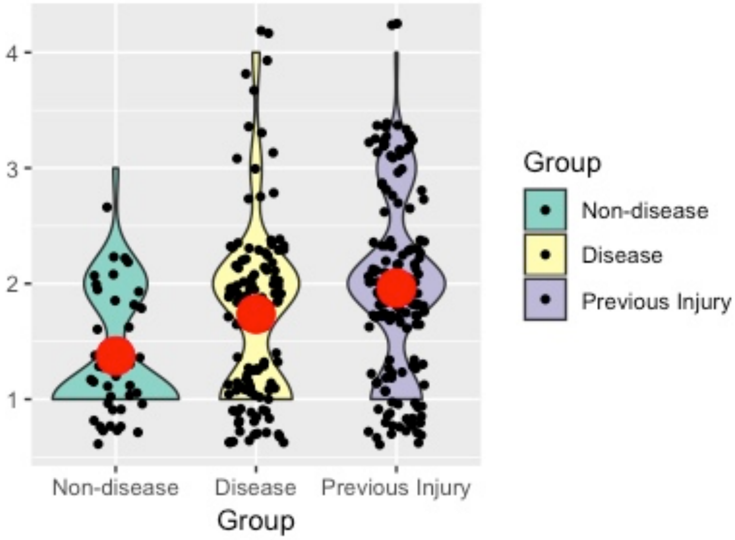


Figure 15. Violin plots illustrating significant differences in the average femur score (red dots) by group.

The frequency of individuals within the cohorts distributed by their femur score descriptions indicate that the disease and previous injury cohorts have the only individuals with ankylosis OA scores (Figure 16).

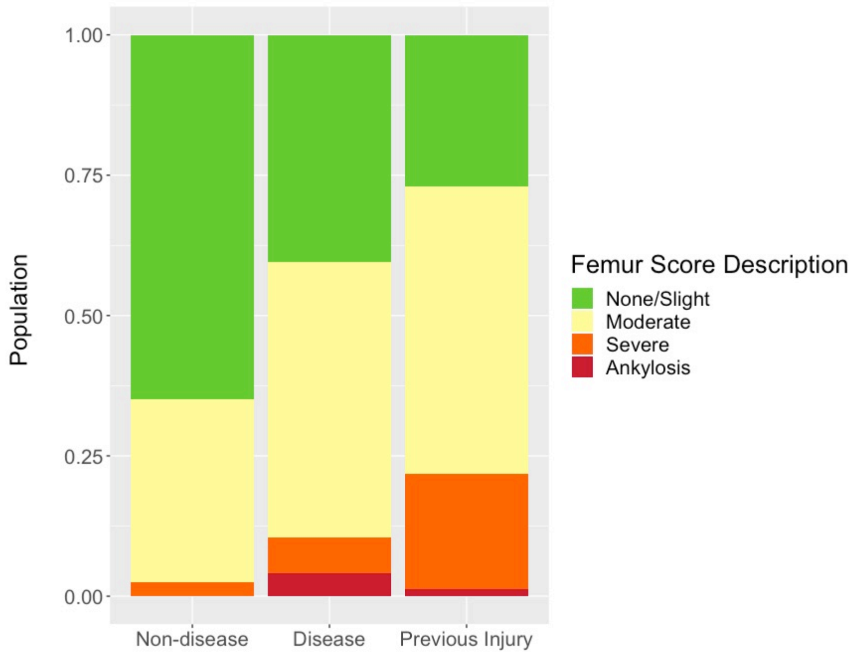


Figure 16. Frequency of individuals in each cohort plotted against OA femur score descriptions (none/slight vs. moderate vs. severe. vs. ankylosis).

The previous injury cohort has the highest percentage of femora scored as severe, and over 60% of individuals in the non-disease cohort have femur scores of none/slight. Figure 17 shows that there are more individuals with a moderate/severe/ankylosis femur score in the disease and previous injury cohorts.

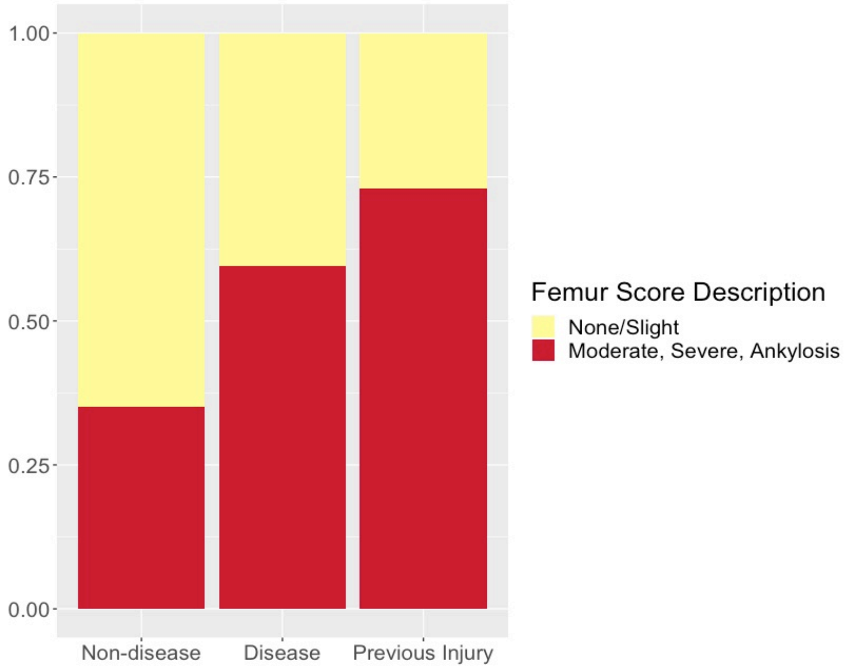


Figure 17. Frequency of individuals in each cohort plotted against OA femur score descriptions (none/slight vs. moderate, severe, and ankylosis).

Results from the binomial logistic regression for the disease cohort reveal that the probability of having OA (moderate/severe/ankylosis) is at most 25% higher than the non-disease cohort, considering the average age. For the previous injury/prosthesis cohort, the probability of having OA is at most 34% higher than the non-disease cohort, considering the average age. For age, each additional year contributes to at most 0.43% more probability of a moderate/severe/ankylosis femur score within a given cohort.

The multilevel binomial logistic regression shows that individuals within the disease cohort are 43% more likely to have OA compared to the non-disease cohort, with age held constant. Individuals within the previous injury/prosthesis cohort are 57% more likely to have OA compared to the non-disease cohort, with age held constant. For age, each additional year to the average age results in 0.7% more likelihood to have OA compared to the non-disease cohort, with group held constant.

Inter- and intraobserver error rates were calculated using Cohen's kappa. The inter-rater reliability as found to be Kappa = 0.452 ($p<0.001$), 95% CI (0.159, 0.746). The results indicate moderate agreement between the two individuals, following Landis and Koch (1977). For intra-observer error, Kappa=1.000 ($p<0.001$), 95% CI (1.000) indicating perfect agreement between the two separate scoring events, following Landis and Koch (1977).

DISCUSSION

The results of the Spearman's rank correlations are consistent with what is known to be true of disease patterns, especially systemic diseases. Individuals both with and without disease had similar left and right femur scores, indicating bilateral symmetry in OA expression (Felson, 1996; Tepper and Hochberg, 1993). However, individuals in the previous injury/prosthesis cohort exhibited differences between their left and right femur scores. This suggests that OA at the hip joint is affected by both injury and prostheses due to specific injuries or prosthesis implants. Individuals in older age cohorts and individuals with systemic diseases, previous injuries, or hip prostheses are at greater risk for developing OA at the hip joint.

An examination of the distribution of OA according to age from this study (Figure 12) suggests that age exacerbates the effects of previous injury, prostheses, and disease on the expression of OA. Individuals in the previous injury/prosthesis and disease cohorts exhibit more severe OA, especially in older age groups, compared to individuals in the non-disease cohorts. This study, combined with recent research (Calce, 2012; Calce and Rogers, 2011; Calce et al., 2017; Calce et al., 2018a; Calce et al., 2018b; Rissech et al., 2006; Rissech et al., 2007; San-Millán et al., 2016; San-Millán et al., 2017; San-Millán et al., 2019; Winburn, 2017; Winburn, 2018), provides evidence in support of further research investigating progressive changes of the hip joint. This investigation could lead to both a better understanding of how OA and aging are related, and could eventually lead to more refined techniques for estimating age-at-death in a forensic context—

perhaps using not only the acetabulum (*sensu* Calce, 2012; Rissech et al., 2006; San-Millán et al., 2017) but also the femoral head.

Both age and orthopedic pathology significantly affected the prevalence of hip OA in this sample. Larger differences between cohorts were seen when the data were analyzed in two groups: none/slight and moderate/severe/ankylosis. This is likely due to the smaller sample size in this study, as large effects were not visible for more extreme expressions of hip OA. Overall, the average femur score for the non-disease cohort was lower than those of the disease and previous injury/prosthesis cohorts. These results support the hypothesis that osteoarthritic changes of the hip are positively correlated with age and prosthesis implants compared to individuals lacking prostheses, and that the prevalence of OA is positively correlated with other systemic diseases. Regardless of the reason for implantation, prostheses alter an individual's gait cycle (Beaulieu et al., 2010). Biomechanical risk factors such as hip morphology (Lespasio et al., 2018; Murray, 1965) are affected by hip prostheses, and any disruption in the joint function could be a catalyst for the development and/or further progression of OA.

Overall, the results of this study show an increase in prevalence of OA for individuals with fractures, both with and without prostheses. Links between OA and systemic diseases were also observed. This is unsurprising considering that systemic diseases, by definition, involve the body as a whole and affect a multitude of biological processes (e.g., BMD, inflammatory stress responses at major joints). Individuals in the disease cohort of this study were primarily diagnosed with metastatic cancer (71%). Medical research has shown that metastatic cancer increases an individual's risk for reduced BMD and fractures (Bremner and Jelliffe, 1958; Drake, 2013; Guise, 2006). Cancer treatments, specifically, alter normal bone processes by reducing osteoblastic activity and increasing osteoclastic activity (Michaud and Goodin, 2006), which leads to cancer treatment-induced bone loss. Given the fact that some previous research links high BMD with increased OA (Barbour et al., 2015; Chan et al., 2014; Dequeker et al., 1995; Lee et al., 2013), these relationships between cancer (and potentially, cancer treatment), decreased BMD, and increased OA are noteworthy, warranting further exploration.

The results of this study are of value to clinicians when considering the necessity for and outcome of total hip arthroplasties and hip prostheses. When skeletally defined, OA is not always a symptomatic disease (i.e., the skeleton does not always correlate with the individual's symptoms during life). For example, an individual with skeletal indicators of severe OA [e.g., receiving a Jurmain (1990) score of 2] may have been asymptomatic during life. This can lead to significant obstacles in detecting the disease early in a clinical context. This research identifies an additional subset of the population who may be at greater risk for developing OA. Individuals who have undergone surgery to implant prostheses at the hip should have altered rehabilitation plans to accommodate for the increased likelihood of developing OA. Research has shown that deviations from normal gait patterns were most prevalent in the operated hip joints (Beaulieu et al., 2010), thus the effects of orthopedic pathology on the prevalence of hip OA is something for clinicians to strongly consider when presented with cases necessitating hip prostheses.

Lack of Population Differences in the Current Sample

Exploratory data analysis also investigated differences in the prevalence of hip OA between males and females, and African- and European-American individuals. Previous studies suggest that females —particularly when obese or elderly—exhibit more OA than males (Coggon et al., 2001; Felson, 1988; Felson and Zhang, 1998; McKean et al., 2007; Winburn, 2017), in spite of the fact that females often suffer from low BMD (Brickley and Waldron, 1998; Burr et al., 1983). However, the current results indicated no differences in femoral OA scores between males and females. Another expectation of the current study was that ancestral differences in OA frequency and progression might be observed between African- and European-American samples. The assumption of ancestral differences in OA patterning is based in large part upon the knowledge that heredity plays an important role in OA proclivity (Cimmino and Parodi, 2004; Spector and MacGregor, 2004). Yet, especially considering the ancestral populations studied herein (people who would have, during life, identified as "black" or white,") another underlying assumption must be scrutinized: that traditional U.S. racial categories reflect hereditary differences in biology that are expressed in both hard-tissue morphology and the processes that affect them. This assumption is typified by the oft-cited trope in biomedical and anthropological research that African-American individuals have higher BMD than European Americans (e.g., Melton, 2001; Melton et al., 2002; Nelson and Megyesi, 2004; Willey et al., 1997). In spite of over a century of research, this theory suffers from inconsistent and uncritical definitions of race, as well as a conflation of hereditary influences on bone health with the production of biological attributes by embodied social factors (Fausto-Sterling, 2008). The uncritical projection of outdated typological thinking onto modern questions of bone health must be questioned. If there really are “racial” differences in BMD and other skeletal attributes, is this due to population-level biology, the lived experience of systemic inequality, or both? And if there are no “racial” differences in skeletal biology, should we instead consider a different framework for comparing skeletal samples, potentially a systems-based approach informed not only by genetics but also by factors like diet, exposure to sunlight, and physical activity which change over the course of an individual’s lifetime (Ahn et al., 2006a,b; Fausto-Sterling, 2008); Wemrell et al., 2016).

Interestingly, this study’s results indicated no ancestral differences in femoral OA scores. While these results must be considered tentative due to small sample size, they contribute to the broader dialogue on biological ancestry, social race, and their effects on skeletal structure. These results are also consistent with a growing body of research indicating that some biological anthropology methods seem to be unaffected by ancestral differences that are expected but not observed (citations). Antemortem demographic data (e.g., height, weight, lifestyle variables) were limited for the current study individuals, but future research should investigate these and other questions on large, diverse, and well-documented skeletal samples.

Inter- and Intraobserver Error

While intraobserver agreement was extremely high in this study, interobserver agreement was only moderate. This discrepancy can be attributed in part to differences in overall experience in recognizing OA and differentiating it from other changes (i.e., lytic lesions, space occupying lesions, etc.) (Ortner, 2003). Both level of education (M.S. vs. Ph.D.) and general professional anthropological practice and training affect individuals' ability to assign scores using more subjective, non-metric techniques (Calce, 2012; Listi and Manhein, 2012; Waldron and Rogers, 1991). Interobserver error rates for anthropological methods based on macroscopic morphological changes can also stem from inconsistent descriptions, which often allow for a high degree of subjectivity during scoring (Calce, 2012; Listi and Manhein, 2012; Waldron and Rogers, 1991). In particular, OA has a wide range of expression and the disease may manifest along a spectrum both within the same individual and between individuals. Previous research on interobserver variation in coding skeletal evidence of OA has found that error rates differ depending on the criteria, with strongest interobserver agreement in recognizing eburnation and new bone on the joint surface (Waldron and Rogers, 1991). Variability in detecting subtle differences in the expression of features of OA is common (Zampetti et al., 2016); and, although the documented error rates are not entirely discouraging, future research should focus on revised feature descriptions in an effort to lower interobserver error rates. Revising current methods for scoring OA (Buikstra and Ubelaker, 1994; Jurmain, 1990) to incorporate more human variation, and improving the diagrams, reference photographs and descriptions offered to capture the range of human variation will lead to an increase in interobserver agreement, and will also allow for a more accurate comparison of results from similar studies (Weiss and Jurmain, 2007). To this end, future should expand the current research and: a) assess the degree of OA in other populations in which there is greater diversity in sex, ancestry, and age; b) observe collections where there are more consistently recorded heights and weights for the sample in order to include BMI in statistical analyses; c) explore the effects of different pathological conditions on OA; and d) explore the effects of OA on different pathological conditions.

Inter- and Intraobserver Error

Disagreement between the inter- and intraobserver errors can be attributed to differences in overall experience in recognizing OA and differentiating it from other changes (i.e., lytic lesions, space occupying lesions, etc.) (Ortner, 2003). Both level of education (M.S. vs. Ph.D.) and general professional anthropological practice and training affect individuals' ability to assign scores using more subjective, non-metric techniques (Calce, 2012; Listi and Manhein, 2012; Waldron and Rogers, 1991). Waldron and Rogers (1991) discuss the implications of interobserver variation in coding osteoarthritis in human skeletal remains. Their skeletal sample consisted of ten specimens; individuals of varying experience and education levels were asked to score the specimens based on the presence or absence of eburnation, marginal osteophytes, new bone on the joint surface, pitting on the joint surface, or deformation of the joint contour. If eburnation was present on the specimen, it was coded as osteoarthritic; however, if eburnation was absent, the specimen was coded as osteoarthritic when at least two of the other criteria were present on the bone. Results indicated that interobserver error rates differed depending on the criteria, with strongest agreement in recognizing eburnation and new bone on the joint surface.

Interobserver error rates for anthropological methods based on macroscopic morphological changes stem primarily from inconsistent descriptions, which often allow for a high degree of subjectivity during scoring (Calce, 2012; Listi and Manhein, 2012; Waldron and Rogers, 1991). Osteoarthritis has a wide range of expression and the disease may manifest along a spectrum both within the same individual and between individuals. Variability in detecting subtle differences in the expression of features of OA (Zampetti et al., 2016) is common; and, although the documented error rates are not entirely discouraging, future research should focus on revised feature descriptions in an effort to lower interobserver error rates. Revising current methods for scoring OA (Buikstra and Ubelaker, 1994; Jurmain, 1990) to incorporate more human variation, and improving the diagrams, reference photographs and descriptions offered to capture the range of human variation will lead to an increase in interobserver agreement, and will also allow for a more accurate comparison of results from similar studies (Weiss and Jurmain, 2007).

Study Limitations and Implications for Future Research

Limitations of this study include the sample size and robusticity of the demographic information available. The Edmonds Orthopedic Pathology Collection at the NMHM from the AFIP is small and, thus, the available sample size and sample diversity (i.e., sex, ancestry, age etc.) could not provide data as abundantly as collections in other recent OA studies (see Wallace et al., 2017; Winburn, 2017). Additionally, antemortem demographic data were not recorded consistently. Due to the paucity of the information available, weight and BMI data could not be used in the logistic regressions.

Therefore, the effects of height and weight could not be investigated for this population with any significance.

These results also support future avenues of research in bioarchaeology and anthropology to develop a more accurate standardized scoring technique for age estimation in a forensic context. In order for such a technique to be precise, however, interobserver agreement for scoring degenerative changes at the hip should increase. Interobserver error is not optimal in studies involving OA; however, this error could be mitigated by revising current techniques in an attempt to reduce the subjectivity of ordinal scoring systems for macroscopic morphological OA scoring techniques. Future studies should expand the current research and a) assess the degree of OA in other populations in which there is greater diversity in sex and ancestry; b) observe collections where there are more consistently recorded heights and weights for the sample in order to include BMI in statistical analyses; c) explore the effects of different pathological conditions on OA; and d) explore the effects of OA on different pathological conditions.

CONCLUSION

The current project considers the intersection of OA and disease, examining the effects of orthopedic pathology on the prevalence of hip OA and leading to a more complete view of the variation in the expression of OA and its multifactorial etiology. In this sample of modern African- and European-American males and females, there were statistically significant relationships between severity of femoral head OA, age at death, history of systemic disease (i.e., metastatic cancer), and evidence of previous injury or prostheses—but no significant sex or ancestral differences in OA prevalence. These findings argue for the relevance of progressive hip-joint changes to anthropological age-at-death estimation. The current results contradict the expectation of population variation in OA expression, indicating that future research should utilize diverse skeletal samples to elucidate the role played by sex and ancestry in OA prevalence and patterning—including how, if at all, BMD affects the progression and expression of OA. The findings that OA progression and expression magnify in individuals with pre-existing systemic diseases, injuries, and surgical interventions also suggest further avenues for research into the prevalence of OA in pathological populations (i.e., whether OA presents as bone formation or degeneration and how it is affected by disease). Researchers of OA must continue to consider pathological populations, or else their results will be of limited relevance for the nearly 20% of individuals in the U.S. living with musculoskeletal diseases (Lawrence et al., 1998).

This study's findings can assist clinicians, bioarchaeologists, and forensic anthropologists in recognizing certain risk factors and biological mechanisms involved in the development of OA. With OA afflicting approximately 54.4 million U.S. adults, and 20-year projections increasing that number to 78.4 million (CDC, 2019), it is crucial that its etiology become better understood. By considering both modern clinical medicine and paleopathological analyses, researchers can disentangle the intricate relationship between OA and its many risk factors. While paleopathology, bioarchaeology, and anthropology are somewhat informed by modern medicine, the fields are entirely separate and approach disease processes differently. The current research bridges that gap and provides a modern example of how orthopedic pathology can impact the prevalence of hip OA. These results have overarching implications for future bioanthropological research within the realms of pathology, skeletal biology, and age-at-death estimation.

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