

**Articular Morphology in Human Limb Synovial Joints: Variation,
Covariation, and Application**

**A Dissertation Presented for the
Doctor of Philosophy
Degree
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DEDICATION

This work is dedicated to the individuals who selflessly donate their bodies to science. Without you, this research, scientific education, and the advancement of our understanding of the human body would not be possible.

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ABSTRACT

Human limb joints are complex skeletal structures that must fulfill the roles of mobility, stability, and articular fit. These roles often place competing demands on joint morphology resulting in trade-offs (e.g., joints allowing greater mobility are usually less stable), but it is unknown how the tension among these antagonistic pressures patterns the morphological relationships within and among our joint surfaces. This dissertation is the first study to analyze intra- and inter-joint variation for all the major joints of the upper and lower limb in the modern human skeleton, and to explore potential applications of the patterns observed.

To address questions of variation, this dissertation takes a 3D geometric morphometric approach by analyzing landmarks placed on the shoulder, elbow, hip, and knee articulations for over 200 skeletons. Results establish a striking pattern of unequal morphological variance in convex vs. concave joint surfaces, potentially indicating differential regulation during development. Covariance analyses suggest that, despite accessory cartilages such as menisci and labra partially accommodating for articular fit, cartilage thickness is unrelated to the strength of correspondence between articulating surface shapes. Furthermore, analogous functional relationships between the humeral and femoral articular surfaces are a stronger source of covariance than direct articulation with neighboring morphologies. Variance-covariance patterns collectively hold clinical implications, as there appears to be opportunity for morphological “mismatch” between articulating surfaces, and in the case of some surfaces, stronger associations with articulations belonging to other joints than with their own complement. With these patterns in mind, the last portion of this dissertation focuses on the knee and determines that distal femur

shape indeed is related to an individual's knee replacement status, a pattern specifically driven by shape qualities of the medial femoral condyle.

These findings contribute to our understanding of morphological trait interdependence, which will hone future evolutionary models, and additionally provides a point of comparison for studies that often focus on linear articular dimensions. By determining the underlying articular shape variation within a single species, this study paves the way for future interspecific studies of joint morphology, development, and locomotion.

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CHAPTER I: INTRODUCTION, BACKGROUND, AND RESEARCH QUESTIONS

Introduction

The existence of biological variation is central to the progression of evolution by natural selection. Exploration into population-level phenotypic variation can reveal information about a species' propensity for adaptation and can be indicative of factors that have structured that variation over evolutionary time. Variation within individuals in a species can indicate patterns established during ontogeny and the postnatal life history of the individual. Variation within and among individuals is a product of gene-by-gene and gene-by-environment interactions manifested through development (Hallgrímsson, Willmore, & Hall, 2002a; Willmore & Hallgrímsson, 2005).

The combinations of shared relationships and/or unique conditions under which limbs exist provide a host of avenues for exploring inter- and intraspecific variation. The vertebrate limb skeleton is a particularly useful vehicle for exploring variation, as bilaterally occurring skeletal elements provide a within-individual opportunity for asking questions regarding bone functional adaptation or developmental stability (Hallgrímsson, Willmore, & Hall, 2002b). Similarly, fore- and hindlimbs are serially linked by similar development (Ruvinsky & Gibson-Brown, 2000; Tickle, 2015; Towers & Tickle, 2009a, 2009b; Young & Hallgrímsson, 2005) yet often experience distinct loading patterns and biomechanical environments due to particular forms of locomotion (Demes et al., 1994; Raichlen, Pontzer, Shapiro, & Sockol, 2009; Reynolds, 1985; Schmitt & Hanna, 2004; Schmitt & Lemelin, 2002).

With the most divergent upper and lower limbs of any primate with respect to function (Rolian, 2009; Young, Wagner, & Hallgrímsson, 2010), humans represent a distinctive

intraspecific case for studying limb variation given the unique trade-offs that accompany bipedal locomotion. The synovial joints of human limbs may have been shaped through trade-offs and constraints that manifest in response to these distinct functional needs to achieve successful alignment of neighboring long bone epiphyses that form a joint. Joint articular surfaces thus achieve their definitive morphologies through a combination of genetic and mechanical inputs (Chijimatsu & Saito, 2019; Frost, 1979; Hamrick, 1999; Plochocki, Ward, & Smith, 2009; Rolfe, Shea, Singh, Bandyopadhyay, & Murphy, 2018; Zhou, 2021), though, as I review below, the process of joint morphogenesis is not well understood (Kan et al., 2013; Pacifici et al., 2005; Pacifici et al., 2006; Zhang et al., 2020). While developmental processes yield stereotypical patterns of conformity and function, researchers have not demonstrated the level of consistency in morphology and conformity required on a local level to achieve consistency in function across a population. How do differences in joint biomechanics or anatomy (such as articular cartilage) permit or inhibit “noise” in articular shape? We can begin to answer these questions by mapping patterns of morphological variation exhibited in articular surfaces and contextualizing expectations and findings based on the individual conditions that characterize each joint.

In this dissertation, I focus on understanding modern human joint shape from the perspectives of variation, covariation, and how variance-covariance patterns relate to joint dysfunction. The three major questions to be investigated here are:

- 1) How is variation in limb joint articular shape apportioned across a modern human population? (Chapter II)
- 2) Do different functional relationships within and among joint articular surfaces produce differential degrees of covariance? (Chapter III)

- 3) Might variation in joint shape predispose members of the population to joint disease and degeneration? (Chapter IV)

Investigating these questions will contribute to knowledge about various topics related to human joints, including how joint shape relates to ranges of motion, the influence of articular cartilage on joint covariation, and how patterns of shape variation relate to the functional differences in the upper and lower limbs.

While the three manuscripts in Chapters II through IV include contextual background, this chapter provides further information about foundational concepts for understanding human limb joints. Topics presented here include an overview of limb development, the effects of mechanical loading on the limb joint from first development through adulthood (including a review of chondral modeling theory), functional relationships among adult joints, and potential sources of variation in joint shape. The final portion of this chapter will detail the materials used in the proceeding manuscripts, as well as the logistics of data collection.

Overview of Limb Bone and Joint Development

Though this dissertation will explore variation in adult limb joints of modern humans, an understanding of limb and joint development and growth is imperative to establish what is currently known about the origins of joint shape and how that shape relates to mechanical load and joint function throughout life. This is in part because adult morphology is inherently an outcome of developmental processes. Though individual contributions of various processes cannot be ascertained (Hallgrímsson et al., 2009) the context of development is essential for setting out hypotheses to be tested with respect to articular surface variance and covariance.

Most bones in the skeleton, including the long bones of the limbs, develop through a process called endochondral ossification. Endochondral ossification (EO) is characterized by the presence of a primary cartilaginous anlage, or template, that is secondarily replaced by bone (Berendsen & Olsen, 2015; Mackie, Tatarczuch, & Mirams, 2011). This process begins in the growing limb buds with the condensation of mesenchymal stem cells, which differentiate into chondrocytes and secrete a cartilaginous matrix to form the template for the future limb bone. Osteoprogenitor cells, precursors to cells that have specialized functions for bone growth and maintenance, differentiate into osteoblasts which subsequently secrete a bony collar surrounding the central diaphysis of the cartilage model in long bones—the primary ossification center—or other primary ossification centers in other elements. Ossification progresses proximally and distally along the cartilage template as hypertrophied chondrocytes undergo apoptosis, while cavitation occurs in the center of the anlage, creating space for newly introduced blood supply and the future medullary cavity (Allen & Burr, 2019; McQueen & Towers, 2020). Vascularization plays an essential role in the progression of ossification along the cartilage anlage, and experimental evidence suggests that the elaborating blood vessels direct ossification via the presence of mineralization-promoting factors that encapsulate the vessels and connect to surrounding epithelial cells (Shoham et al., 2016).

Secondary ossification centers arise at the ends of the cartilaginous template and will form the future epiphyses (Allen & Burr, 2019; McQueen & Towers, 2020). The metaphysis—a growth plate of cartilage—is preserved between the ossifying shaft and bone ends to accommodate longitudinal growth. This growth plate persists until the primary and secondary ossification centers meet and fuse together, indicating skeletal maturity. Cartilage is maintained on the articular surfaces of epiphyses throughout life unless joint disease or degeneration occurs.

Early in the process of EO, joints emerge as interruptions or discontinuities in the cartilaginous anlagen (Chijimatsu & Saito, 2019; Xie & Chagin, 2021). As condensed mesenchymal cells begin to differentiate into chondrocytes, mesenchyme between the developing bones does not differentiate, creating a distinction between the limb segments and marking the location of the future joint (Chijimatsu & Saito, 2019), the interzone. The interzone mesenchyme forms a dense connective tissue, which interacts both through molecular induction and mechanical movement with future articular surfaces of the bone anlage to differentiate into articular cartilage. This articular cartilage does not ossify during EO, but will persist as the dense tissue that pads bone ends during life. Regulated cell death in the interzone mesenchyme creates the synovial cavity, while the mesenchyme becomes the joint capsule, any cartilaginous elaborations such as menisci, and the enclosed joint ligaments (Chijimatsu & Saito, 2019).

Interzone genesis and maintenance is a highly regulated sequence of events that depends on many genetic factors. Like limb bone morphogenesis in general (see Tickle 2015), the interaction of multiple genes, differential time and regulation of expression, and environmental factors combine to determine synovial joint morphology. As a regulator of downstream development, growth differentiation factor 5 (*GDF5*) is one of the most critical contributors to healthy joint formation. Researchers have demonstrated its importance in interzone development and maintenance through murine experimental studies, which have revealed *GDF5* to be causal for brachypodism and affect joint morphology (Storm et al., 1994). Some studies suggest *GDF5* plays a role in articular cartilage production *in vitro* and *in vivo* (Coleman et al., 2013; Francis-West et al., 1999; Tsumaki et al., 2002), but detailed research has shown that *GDF5* disappears prior to the formation of cartilage during development and therefore is likely not responsible for articular cartilage formation (Chijimatsu & Saito, 2019). Nonetheless, cells that express *GDF5*

will ultimately give rise to all the tissue components of the adult knee, for example, such as menisci, ligaments, and synovium (Chijimatsu & Saito, 2019; Rountree et al., 2004). In humans, *GDF5* mutations can result in brachydactyly (Polinkovsky et al., 1997) and chondrodysplasia (Thomas et al., 1997; Thomas et al., 1996). Other factors such as *Wnt* and *Gli*, among others, are also consequential for the developing joint and likely interact with *GDF5* (Akiyama et al., 2015; Rolfe et al., 2018) in combination with sufficient mechanical input, though the precise mechanisms of joint morphogenesis await further research outcomes.

The Effects of Mechanical Loading on Developing and Definitive Joint Anatomy

Mechanical loading is influential for joints in all phases of life. Mechanical loading on the limbs is crucial for healthy joint development. Postnatally and into adulthood, loading has heterogeneous implications for the limb skeleton. This section details the influence of mechanical loading on joints (relative to limb bone diaphyses), from its crucial role in joint morphogenesis to its effects in adulthood.

Loading in Utero and Implications for Joint Morphogenesis

In addition to the cellular pathways promoting chondrocyte maturation and progression of EO, mechanical loading plays an essential and complementary role in cartilage and bone formation with explicit implications for joint articulations (Nowlan, Sharpe, Roddy, Prendergast, & Murphy, 2010; Rolfe et al., 2018; Shea, Rolfe, & Murphy, 2015; Singh et al., 2018). A developing fetus does not experience the same types of mechanical loads as an adult. Nevertheless, strain still acts on the developing skeleton, taking the form of quick, involuntary muscle contractions related to limb movements and stretching, which can be observed starting

around ten weeks gestation (De Vries & Fong, 2006; De Vries, Visser, & Prechtl, 1982). Though controversial, some researchers suggest that such movement is essential for the formation of concave and convex surfaces on bone (Carter & Wong, 1988; Nowlan, Murphy, & Prendergast, 2007; Stevens, Beaupré, & Carter, 1999; *cf.* Khayyeri, Isaksson, and Prendergast, 2015; Xie and Chagin, 2021), but experimental research provides uncontroversial support for the importance of movement for normal limb long bone formation.

Experimental studies have identified broad consequences of immobilization *in utero*, including lack of joint cavity formation, malformed or non-interlocking articular surfaces, and muddled tissue region definition in the developing limb (Akeson, Amiel, Abel, Garfin, & Woo, 1987; Drachman & Sokoloff, 1966; Kahn et al., 2009; Mikic et al., 2000; Roddy, Prendergast, & Murphy, 2011). To better understand the specific molecular pathways that are induced by mechanical stress and strain, Rolfe et al. (2018) analyzed paralyzed limbs in mouse embryos and found they exhibited a reduction in *Wnt* activity at the future joint site as a result of the paralysis. The lack of mechanical stimulation and resulting reduction in *Wnt* activity prevented differentiation between the cartilage of the bone anlage of its articular surface, which under normal circumstances would begin to exhibit joint-establishing markers such as *GDF5* (Chijimatsu and Saito 2019). Because there was no distinction between the adjacent chondrocytes, Rolfe et al. (2018) found that the presumptive interzone mesenchyme did not undergo stereotypical formation (with cell differentiation and apoptosis to form a synovial cavity), but instead did not differentiate and ossified along with the anlage, resulting in total fusion of the limb with no joint formation. This study, among others (Giorgi, Carriero, Shefelbine, & Nowlan, 2014; Heegaard, Beaupre, & Carter, 1999), demonstrate that joint

morphogenesis emerges from critical interactions between the molecular and biomechanical environment.

Despite the growing understanding of morphological implications for lack of movement *in utero*, the exact mechanisms for joint shape formation continues to remain elusive. As noted above, various computational models of joint morphogenesis have been proposed to explain the developmental growth patterns that result in the convex and concave shapes found in articular surfaces. The first such models were advanced by Heegaard et al. (1999) and Stevens et al. (1999) with a specific focus on the mechanobiological effects of muscle and tendon contractions on developing epiphyses. More recently, models have focused on how various patterns of hydrostatic stress are responsible for articular topography (Giorgi et al., 2014). These models are not uncontroversial, however, as they are difficult to validate experimentally, and in experimental corroboration they are inherently made obsolete (Khayyeri, Isaksson, and Prendergast, 2015). Nevertheless, such *in silico* models provide a framework of falsifiable hypotheses. Despite evidence from both models that articular surfaces do exhibit morphogenic responses to loading, the models fail to achieve proper surface congruency, suggesting a latent contributor remains unaccounted for in joint morphogenesis, which may be in part resolved through chondral modeling theory.

Postnatal Loading and the Chondral Modeling Theory

As sites of interaction between the long bones of the limbs, joint surfaces must achieve a coordinated, targeted postnatal growth that ultimately produces congruent definitive articular surfaces, yet also maintains surface congruence as well as structural and functional integrity of the joint complex throughout all stages of postnatal growth. To date, the most comprehensive

model for describing this dynamic growth trajectory has been the chondral modeling theory (Frost, 1979; Hamrick, 1999). Chondral modeling theory posits that local variation in hydrostatic pressure will shape the growing joint, whereby portions of the joint surface that experience 1–10 MPa of hydrostatic pressure will expand, while growth is inhibited in the portions of the articular surface experiencing pressures above or below that range. Because the surface portions experiencing lower pressure will be those that are not yet conformed to the opposing articular surface, the resulting expansion that occurs here causes the surfaces to grow to meet one another; conversely, pressure exceeding the set range is observed in the portions of the joint that are already in contact, and growth here is thus limited (Hammond, Ning, Ward, & Ravosa, 2010; Hamrick, 1999; Lee & Bader, 1997; Plochocki et al., 2009; Takahashi et al., 1997). Over time, this growth model produces patterns of increasing joint surface congruence, a reduction in the severity of the articular surface curvature and contours, and a decrease in the size of the epiphysis relative to the long bone (Plochocki et al., 2009).

Cellular mechanisms by which hydrostatic pressure can implement differential cartilage proliferation have been identified (Congdon, Hammond, & Ravosa, 2012; Lee & Bader, 1997; Takahashi et al., 1997), though the evidence for chondral modeling most relevant to this dissertation involve the macroscopic joint patterns. Sylvester (2015) provides a salient example in an analysis of ungulate joint contours, which were previously thought to be almost perfectly circular in shape and thus would exhibit consistent radii of curvature of their femoral condyles (Freeman, 2001; Heiple & Lovejoy, 1971; Lovejoy, Cohn, & White, 1999; Tardieu, 1981). Sylvester analyzed the femoral radii of curvature of eleven ungulate species, finding that not only did they exhibit varied radii, disproving previous assumptions, but also that the flatter portions of the joint surface corresponded directly with peak ground reaction forces experienced

by the joint during locomotion. These findings provide support for the chondral modeling theory and suggest that gross joint shape can be indicative of function and the forces that potentially shape the articulation.

The evidence for chondral modeling has not been unequivocal, however. Studies by Hammond et al. (2010) and Congdon et al. (2012) were some of the first to investigate the occurrence of chondral modeling occurring *in vivo* using a sample of pigs experiencing adolescent growth. Subgroups of the pigs were subjected to a repeated exercise regimen over the course of 17 weeks, while the remaining pigs acted as a sedentary comparison group. Hammond et al. (2010) studied the growth plate, articular cartilage, and bony anatomy of the femur to determine if exercise greatly affected these regions relative to the sedentary group. While differences were noted between the two experimental groups presumably related to their exercise regimens, there were heterogeneous effects of loading among cartilaginous growth regions. The metaphysis of the developing femora exhibited a greater response to exercise than the cartilage at the articular surface of the joint, which is classically regarded as the main location undergoing chondral modeling. This heterogeneity in cartilage response to loading was corroborated by a later study (Congdon et al., 2012), which expanded to include analysis of the humerus, given that the forelimb is the main load-bearing limb in pigs. The authors found that the cellular responses predicted by chondral modeling theory (increases in chondrocyte proliferation and area, as well as an increase in the production of extracellular matrix) were only partially observed among cartilage regions—articular cartilage exhibited increased chondrocyte proliferation but metaphyseal cartilage increased chondrocyte area in response to loading. Congdon et al. (2012) posited that differences in cartilage composition between the two sites may yield different response thresholds and called for predictions from chondral modeling to consider this

possibility, though future studies should also investigate the possibility that the loading regimes placed on the test subjects may have been insufficient to produce a response.

In addition to a potential threshold effect as posited by Congdon et al. (2012), the developmental window for modeling of cortical bone on articular surfaces may be limited and heterogeneous across the skeleton. Terhune, Sylvester, Scott, and Ravosa (2020), for example, showed that trabecular architecture of mandibular condyles in rabbits reflected loading in response to dietary variation, but there was no difference in condylar shape. Other aspects of cranial anatomy have demonstrated remodeling in response to masticatory loading, however, and coupled with trabecular bone response these results caution against generalizing osteogenic responses to mechanical stimuli from a single skeletal element, let alone a single dimension or part of that element (Terhune et al., 2020).

The literature on chondral modeling seemingly presents an incomplete picture of the phenomenon of postnatal articular growth. While gross morphological patterns appear to align with the expectations of chondral modeling (Sylvester, 2015), the cellular mechanisms through which these patterns manifest are ambiguous and non-homogenous among cartilaginous regions of a growing limb bone (Congdon et al., 2012; Hammond et al., 2010), and may be varied across the skeleton. While chondral modeling remains the most comprehensive theory to date to describe joint growth's response to loading, future studies are needed to acquire more micro- and macroscopic evidence.

Mechanical Loading in Adulthood and Bone Functional Adaptation

Bone functional adaptation, first described by Carter and Orr (1992) and later popularized by Ruff, Holt, and Trinkaus (2006) as a modern interpretation of Wolff's Law (Wolff, 1892),

refers to the propensity for bone to respond and remodel to accommodate mechanical loading patterns over an individual's lifetime. The cellular mechanisms of bone functional adaptation rely on the principles advanced in Harold Frost's Utah Paradigm (Frost, 2001), later reorganized into the mechanostat model for bone homeostasis (Frost, 1987; Lerebours & Buenzli, 2016). Broadly, the mechanostat is based on a minimum range of loading that is required to maintain bone health. Bone experiencing consistent loading regimes below or in excess of this baseline range of structural resistance will exhibit a cellular remodeling response that leads to morphological alterations to the bone over time (Frost, 1987; Lerebours & Buenzli, 2016). This geometric alteration maintains efficient load-bearing and tissue conservation. There is experimental evidence that new bone cells that form in response to load-induced remodeling will already be calibrated to the current mechanical environment, contributing to a local bony architecture that is completely adapted to the increased loading regimes and no longer in need of adding or resorbing additional bone (Lerebours & Buenzli, 2016). In other words, the addition of bone in response to the loading environment will plateau over time as new cells are added with adjusted strain thresholds, producing a new baseline mechanical range for maintaining bone levels.

The bone functional response has been shown to produce significant differences in bone dimensions between individuals experiencing distinct biomechanical environments, or between antimeres within the same individual (Agostini, Holt, & Relethford, 2018; Blackburn, 2011; Nadell & Shaw, 2016; Plochocki, 2004; Shaw & Stock, 2009a, 2009b; Trinkaus, Churchill, & Ruff, 1994). As the main site of long bone bending during activity and locomotion, limb bone diaphyses are a prime location for detecting adaptation-induced variation. Major diaphyseal patterns include larger right-side dimensions, especially in the upper limb, often with

contralateral dominance in the lower limb (Auerbach & Ruff, 2006; Ingelmark, 1974; Plochocki, 2004; Ruff & Jones, 1981; Sakaue, 1998; Schultz, 1937; Trinkaus et al., 1994).

Despite these well-established patterns of adaptation that manifest in limb bone diaphyses, there is limited evidence to suggest that coordinated adaptive responses occur in the external shape or cortical bone of articular surfaces. It is possible that this is due in part to differences in the way the diaphysis and epiphyses receive and transmit load. Under normal locomotory circumstances, diaphyses are subjected to bending moments while the epiphysis and joint surfaces experience compression (Carter & Hayes, 1976; Currey, 2002; Hayes, 1991). As locomotion develops over an individual's lifetime, the associated loading regimes shape the patterns observed in the diaphysis and epiphyses. The most conspicuous alteration to the diaphysis over ontogenetic time is the lengthening of the diaphysis associated with endochondral ossification. With this lengthening, the mid-diaphyseal cross-section also experiences appositional growth, whereby the diameter of the limb bone increases in concert with the bone's length to maintain its strength against bending moments (Ferretti, 1995). Without this appositional growth acquired through bone functional adaptation, the limb bone length to diameter ratio would increase, resulting in a greater likelihood of the bone failing under the normal bending conditions experienced during locomotion (Currey, 2002).

Two studies of marked significance to this dissertation were designed to specifically address bone functional adaptation in joint articular surfaces, yet these studies present conflicting results. Both Lieberman, Devlin, and Pearson (2001) and Plochocki (2004) analyzed articular differences between active and sedentary groups, with Lieberman et al. examining sheep subjected to loading regimes of various intensity, and Plochocki comparing human athletes to non-athletes. Lieberman et al. (2001) found no significant articular differences between sheep

subjected to repeated exercise and sheep not treated with exercise. Their study is regarded as strong evidence for low responsiveness or high restriction in articular surface cortical morphology to loading and contributes to a body of work that advances a model of articular constraint (Auerbach & Ruff, 2006; Lazenby, Cooper, Angus, & Hallgrímsson, 2008; Ruff, 1994, 2002). The articular constraint literature suggests that articular surfaces have limited ability to exhibit a functional adaptation response due to the need to maintain structural integrity of the joint and its surrounding soft tissues. Furthermore, these studies make direct comparisons to diaphyseal and trabecular responses to loading by demonstrating the expected patterns of adaptation occurring in these locations despite the lack of response in the articular surface (Lazenby et al., 2008; Lieberman et al., 2001).

In contrast to the results observed by Lieberman and colleagues, Plochocki (2004) found human articular variation to mimic the aforementioned side-biased patterns that are well-established for limb bone diaphyses, which implies that lateralized behaviors may exert influence on both epiphyses and diaphyses and argues against the low response observed in the experimental sheep by Lieberman and colleagues. Research design differences—including the use of quadrupeds versus bipeds, the nature of the exercise used in each study, and the potential for longer-term asymmetric loading in humans—could have contributed to the apparent contradictions in study conclusions. Given that humans exhibit side-biased activity associated with handedness that is enculturated from a young age (Blackburn, 2011; Blackburn & Knüsel, 2006; Shaw, 2011; Steele & Mays, 1995), it is possible that they already have a greater propensity for articular differences than quadrupedal sheep whose limbs experience more evenly dispersed locomotor activity. This difference in the functional diversity of the subjects' limbs perhaps explains the contradictory findings. Further, these two studies utilized linear dimensions

of articular surfaces which may be inadequate to capture the nuances of joint surface variation. Nevertheless, it is notable that two studies designed to assess functional adaptation, specifically in articular cortical dimensions, arrived at opposing conclusions regarding the ability of the epiphyses to reflect activity.

The debate regarding the ability of the articular surface to exhibit load-induced remodeling throughout life remains contentious, as reviewed above. At minimum, we may hypothesize from other studies that any cortical changes that may be happening at the epiphyses, outside of those occurring during specific developmental windows through chondral modeling, are much less conspicuous than those which accumulate in other long bone regions such as the diaphysis. This heterogeneity of load response suggests that patterns of variation observed in the articular surfaces are likely to differ from those that are well-established for the diaphyses.

Clinical Effects of Lifetime Joint Loading

One of the most common afflictions in the United States today is degenerative joint disease. Arthritis—a subcategory of rheumatic disease that affects only the joints and connective tissues of the skeleton—can take many forms, but the most common form is osteoarthritis (United States Bone and Joint Initiative, 2018). Osteoarthritis (OA) is predominantly characterized by the destruction of articular cartilage, and in severe cases, damage to and breakdown of the underlying subchondral bone. It commonly affects the joints of the lower limb, the wrist and hand joints, and articulations in the cervical and lumbar regions of the vertebral column (Cushnaghan & Dieppe, 1991). While there are many underlying factors that may predispose and individual to developing OA, such as obesity, injury, bone density, and sex (Zhang & Jordan, 2010), as well as genetic variations (e.g., Ehlers-Danlos Syndrome; Reinstein

et al. 2013), repetitive biomechanical loading of joints throughout life is often regarded as a primary driver of OA (Guilak, 2011; Herzog, Adams, Matyas, & Brooks, 1993; Sun, 2010; Valderrabano, Horisberger, Russell, Dougall, & Hintermann, 2009). The innate structure of articular cartilage and its role in creating low-friction environment for joint movement makes it relatively impervious to repetitive loading from locomotion and other activities (Currey, 2002; Martin et al. 2015), however it can begin to exhibit wear over time. The articular cartilage's lack of vascularization means that the tissue is unable to heal once injury has occurred or wear has commenced (Sutherland, Converse, Hopkins, & Detamore, 2015). After the onset of articular cartilage degeneration, biomechanical loading only exacerbates the problem and can accelerate OA symptoms and/or the need for a total joint replacement (Benders et al., 2013).

Individuals exhibiting malalignment of their joints, for example clinical varus or valgus knees, may experience abnormal load transmission through their joint which can ultimately contribute to OA. During normal knee joint loading, forces are highly localized on the medial femoral and tibial condyles (Andriacchi, 1994; Brouwer et al., 2007; Morrison, 1970). Individuals presenting with a varus or valgus malalignment to their knee may see an increase in force transmitted through the medial or lateral knee structures, respectively (Sharma et al., 2010), and this altered axis of loading has been tied to increase OA onset and progression (Cerejo et al., 2002; Elahi, Cahue, Felson, Engelman, & Sharma, 2000; Sharma, 2007; Sharma et al., 2010). The deleterious effects of knee malalignment on joint health are magnified in individuals exhibiting other risk factors such as obesity (Brouwer et al., 2007).

Given that the angle with which the femur and tibia articulate with one another can alter normal load burdens on the joint and impact an individual's likelihood of developing OA, it is possible that the shape of the tibiofemoral articulations may play a role in this relationship as

well. Attempts have been made to identify clinical knee morphologies that predispose individuals to OA and have shown that knee shape can be associated with OA status (Gregory et al., 2007; Haverkamp, Schiphof, Bierma-Zeinstra, Weinans, & Waarsing, 2011; Lynch et al., 2009; Morales Martinez et al., 2020; Wise et al., 2018); yet identifying the local shape differences in the articulations that are driving this association has proven difficult and requires further study.

Functional Relationships Among Joints

Perhaps the most pressing demand on joint shape is that of complementary growth and function between directly articulating surfaces. As discussed in the previous sections, for the joint to fulfill its functional role, its articular surface shapes must achieve growth that results in some degree of shape conformity. If joint shapes fail to form properly during development, joint shape, and as a result, joint function is severely hampered (Akeson et al., 1987; Drachman & Sokoloff, 1966; Kahn et al., 2009; Mikic et al., 2000; Roddy et al., 2011). Given the high stakes often associated with joint malformation or malalignment, achieving complementary function is presumably a strong driver of shape correspondence between directly articulating structures. However, the role of articular cartilage in joint conformity cannot be ignored. All synovial joint articular surfaces are covered in a thin layer of hyaline cartilage that is between approximately 2 and 4 mm in depth that, in conjunction with synovial fluid, facilitates low-friction motion between articulating surfaces (Mow, Gu, & Chen, 2005; Sophia Fox, Bedi, & Rodeo, 2009). Some joints exhibit additional fibrocartilaginous elaborations (e.g., the labra of the shoulder and hip, the menisci of the knee), which are responsible for a combination of functional roles

including load diffusion (Ahmed, Burke, & Yu, 1983; Fairbank, 1948; Fukubayashi & Kurosawa, 1980; Gee & Posner, 2021), enhancement of congruence between articular surfaces (Almajed, Hall, Gillingwater, & Alashkham, 2022; McDermott, Masouros, & Amis, 2008; Walker & Erkman, 1975), and stabilization of joint excursion (Almajed et al., 2022; Bendjaballah, Shirazi-Adl, & Zukor, 1998; Levy, Torzilli, Gould, & Warren, 1989; Levy, Torzilli, & Warren, 1982; Shoemaker & Markolf, 1986). These additional cartilaginous structures vary in shape, size, and depth depending on the joint, and some synovial joints such as the elbow altogether lack such elaborations of fibrocartilage. Though the presence of fibrocartilage is understood to partially accommodate for articular fit, the potential for an inverse association to exist between the amount of cartilage present in a joint and the degree to which the joint's articular surface shapes correspond to one another has not been explored.

In addition to the complementary functional relationships that exist between the articulating surfaces of a joint, there exist functionally analogous relationships between surfaces in the upper and lower limb. Functional analogy (see, for example, Schmidt and Fischer, 2009) between skeletal elements refers to similarities in permitted mechanical movement and, in the case of joints, articular surface shape. Researchers often group joints into categories based on the particular types of movement they are capable of producing, as well as the range of motion they can exhibit in any one direction. Joint movement is often quantified using degrees of freedom (DOF), the number of unique movements available at a joint (Currey, 2002). Any two articulating structures, in theory, have the potential to exhibit up to six possible DOF (three translations and three rotations). Yet given the unique morphologies and surrounding soft tissues that facilitate stability at each joint, all joints are restricted to fewer than six DOF under non-pathological, non-traumatic circumstances. Three of the four joints of interest in this dissertation

exhibit three DOF—the shoulder, hip, and knee all experience 1. Flexion/extension, 2. Abduction/adduction (this manifests as mediolateral translation for the knee), and 3. Internal/external rotation. Likewise, the elbow experiences three DOF (1. Flexion/extension, 2. Abduction/adduction, and 3. Pronation/supination); however, this dissertation excludes the humeroradial portion of the elbow joint that is responsible for pronation/supination, leaving two humeroulnar DOF to be analyzed for the purposes of this study.

Despite similarity in number of DOF among the major joints of the limbs, the same DOF produces different ranges of motion for each articulation. For example, both the shoulder and the knee can rotate, but the shoulder can accommodate approximately 153 degrees of rotation while the knee can only rotate approximately 70 degrees. Similarly, while the knee joint is capable of abduction/adduction as the shoulder and hip, its medial and lateral displacement during this movement has been recorded as less than 2mm (Li et al., 2009), and is therefore not a prime role for this joint. Given the limited amount of rotation and abduction/adduction available at the knee, presumably this DOF will exert a reduced influence on joint morphology than will a major movement such as flexion/extension.

Joints capable of specific ranges of motion have general shape features that contribute to their ability to allow or disallow movement in any given direction and are commonly classified into relative shape categories. The shoulder and hip, for example, are considered ball-and-socket joints qualified by high multidirectional excursion, making them the highest range of motion joints in their respective limbs. As such, the individual articular components of these ball-and-socket joints perform similar roles, making the glenoid fossa functionally analogous to the acetabulum, and the humeral and femoral heads analogous to one another. Likewise, because the highest degree of excursion exhibited by the elbow and knee occur in a single plane

(flexion/extension), they are both considered hinge joints. Functional analogs within the hinge joints are the distal humerus and distal femur, which both exhibit rounded condylar articulations, and the ulnar semilunar notch and tibial condyles, which rotate about those distal articulations, respectively.

Gross features of joint shape have been linked to function and movement (Martelli & Pinskerova, 2002; Sylvester, 2015), and therefore the similarity in function and movement between limb joints may influence shape covariance in analogous structures. However, analogous surfaces are subject to distinct loading patterns and biomechanical environments given their membership to different limbs, thus the relationship of functional analogy is presumably less influential on shape associations than the more local demand of direct articulation and complementary function. Some of these sources of variation in articular shape are considered below.

Potential Sources of Variation in Human Articular Shape

Studies mentioned previously (Martelli & Pinskerova, 2002; Plochocki, 2004; Plochocki et al., 2009; Sylvester, 2015) collectively illustrate that there are both kinematic and ontogenetic factors that shape morphological variation manifest at the joint surface. What is currently known about limb joint variation largely comes from studies using linear dimensions. Clear and consistent patterns of dimensional variation repeatedly observed in limb bone diaphyses (Auerbach & Ruff, 2006; Ingelmark, 1974; Plochocki, 2004; Ruff & Jones, 1981; Sakaue, 1998; Schultz, 1937; Trinkaus et al., 1994), as well as trabecular bone within epiphyses (e.g., Terhune et al., 2020)—patterns that provide support for adaptation in response to mechanical loading

during life. However, the evidence for variation in the articular surfaces is more contentious, as reviewed above (Lazenby et al., 2008; Lieberman et al., 2001; Plochocki, 2004). Some of the disagreement could be a consequence of the use of linear measurements in these studies, which largely captures information about size. Yet epiphyseal surface variation is manifest by shape and size, and so examinations of both would prove more informative to our understanding of joint variation than measures of size. Herein, then, I consider potential sources of both size and shape variation based on the previous studies. These potential contributing factors to joint shape variation will be the focus of the main research studies in subsequent chapters.

Sex

Sexual dimorphism, specifically in body size, is one of the most conspicuous sources of intraspecific variation across all biological organisms (Abouheif & Fairbairn, 1997; Fairbairn, 1997; Frayer & Wolpoff, 1985; Herczeg, Gonda, & Merila, 2010; Prenter, Elwood, & Montgomery, 1999; Rensch, 1950; Smith & Cheverud, 2002; Stephens & Wiens, 2009; Szekely, Freckleton, & Reynolds, 2004). While body size includes soft tissue factors like differential distribution of fat between males and females, methods designed to estimate an individual's sex strictly from skeletal material predominantly employ size differences in morphological or metric traits with relative success (Giles & Elliott, 1963; Shearer, Sholts, Garvin, & Warmlander, 2012; Spradley & Jantz, 2011; Walker, 2008). Sexual size dimorphism has the tendency to overwhelm variation arising from other biological sources, and so studies that control for size in their examinations of morphology (e.g., through Procrustes transformations of three-dimensional morphometric data) can minimize the impact of size as a source of variation.

A comprehensive shape comparison between male and female joints has not been conducted, but sexual dimorphism is known to occur in joint architecture, such as the carrying

angle of the elbow and the quadriceps angle of the knee, though evidence is mixed. The carrying angle of the elbow is the obtuse angle formed by the lateral deviation of the forearm relative to the main axis of the arm. Females have been observed as having greater carrying angles than males (Kazi, Keche, Joshi, & Wanjari, 2017; Kothapalli, Murudkar, & Seerla, 2013; Ruparelia, Patel, Zalawadia, Shah, & Patel, 2010), though some studies report no significant differences between the sexes (Kumar et al., 2010; Sharma, Jabeen, Magotra, & Choudhary, 2019). The quadriceps angle is an often-cited joint related difference between males and females measured at the intersection of two lines, one running from the anterior superior iliac spine (ASIS) of the os coxa to the patella, and the other extending from the patellar center to the tibial tuberosity (Grelsamer, Dubey, & Weinstein, 2005). Researchers have hypothesized that the wider relative pelvic width in females alters this geometric relationship between the hip and knee in a way that requires morphological accommodation at the joint surface, though studies directly assessing articular surface morphology are rare. A study by Grelsamer et al. (2005) addressed the more proximate source of variation by exploring whether the quadriceps angle truly differs between males and females. Using anteroposterior X-rays, Grelsamer et al. measured distance between the left and right anterior superior iliac spines and discovered that hip width would need to increase by approximately 9 cm to change the quadriceps angle by five degrees, suggesting that the normal range of variation that occurs in male and female hip width is likely not inducing significant differences in the quadriceps angle, or further, in knee morphology. When the individuals in the sample were controlled for height, no significant differences in the quadriceps angle were observed. Grelsamer et al. (2005) concluded that stature is the main contributor to an individual's quadriceps angle, and because stature is a moderately sexually dimorphic trait, it creates the appearance of sexually dimorphic quadriceps angles.

The documented trends in carrying and quadriceps angles may simply be a product of size rather than true shape differences. However, if sex-related shape differences do exist in joint articulations they are perhaps most likely to occur in the elbow and knee, given that the carrying and quadriceps angles are thought to accommodate for larger pelvic breadths (Kothapalli, Murudkar, & Seerla, 2013; Raizada, Shruthy, Takiar, & Bhuvanesh, 2019), though this hypothesis is nuanced. Males have larger absolute bi-iliac breadths than females from the same population, however it is the *relative* ratio of bi-iliac breadth to stature and body size that is larger in females. Human males are only approximately 9% taller and 15% heavier than females (Sulp & Barrett, 2014) creating a large overlap in body size between the sexes. Because a “larger” female pelvis is relative to and predicated on other body size measures, it is possible that controlling for body size will eliminate any nuances of sexual dimorphism in the joints, reinforcing the findings by Grelsamer et al. (2005).

Chondral modeling

In a previous section, I described the chondral modeling theory of joint elaboration during postnatal growth, originally proposed by Frost (1979) and later re-evaluated by Hamrick (1999). Various studies have found macroscopic, shape-based evidence that supports chondral modeling in other species; for example Sylvester (2015) linked the varying radii of curvature of ungulate femoral condyles directly to specific moments in their loading cycle during locomotion. While much of chondral modeling research has taken place on non-human quadrupeds, humans are also known to exhibit an inconsistent radius of curvature in their femoral condyles resulting in an articular surface that is anteriorly flatter (e.g., exhibits a greater radius of curvature) than the posterior portions of the condyles. Taken together with a study conducted by Martelli and Pinskerova (2002), which found human femoral condylar morphology to associate with specific

moments in the knee's range of motion, a case emerges for the applicability of chondral modeling to human joints. If chondral modeling does in fact describe the process of joint elaboration during human postnatal growth, we may expect to see differences in articular shape variation between left and right joint surfaces in a population. Human lower limbs are wholly responsible for locomotion while human upper limbs have been released of locomotory obligations and can engage in myriad activities. Such activities are often side-biased due to individual handedness that is enculturated from a young age (Auerbach and Ruff, 2006; Blackburn, 2011; Blackburn & Knüsel, 2006; Shaw, 2011; Steele & Mays, 1995). Given that chondral modeling relies on biomechanical pressure patterns to promote or inhibit articular growth, the lateralization and preference for limb use, especially in the upper limb, could plausibly produce differential patterns of variance between antimeres. Likewise, the less lateralized repetitive motions of locomotion and load bearing occurring in the lower limb might produce more consistent variation between the lower limb joints.

Other Factors: Range of Motion and Articular Cartilage

One of the major differences in how joints function relative to one another is the range of motion each joint can perform. An overview of degrees of freedom and joint types (e.g., ball-and-socket vs. hinge joints) was presented in the previous section of this chapter, though these differences presumably have implications for joint shape. A high range of motion joint can exert greater excursion in more directions. Because this translates to a need to meet a multitude of functional demands, it is possible that these various functional requirements result in a morphological stasis, preventing articulations from varying greatly so as not to interfere with its many functional roles. Alternatively, if the morphology of lower range of motion joints is meeting fewer functional demands in the form of low excursion or fewer degrees of freedom,

there may be greater tolerance of variation that accrues in these joints; in other words, morphological variation in lower range of motion joints may incur less cost in movement, and therefore may have greater variance relative to high range of motion joints.

The presence and composition of accessory joint cartilages like the labra and menisci were described above and cannot be ignored when making predictions regarding articular variation. Among other biomechanical roles, accessory cartilage provides partial accommodation between articular shapes to enhance their surface area of contact. Because the cartilage contributes to articular fit, this presumably relaxes the need for full congruence between the bony components alone. If this is the case, then joints exhibiting very little accessory cartilage must achieve much of the joint's congruence with the articulations alone, whereas a joint with more extensive accessory cartilage would be more tolerant of variations in articular shape of its bony components. This inverse relationship predicts that the knee exhibits the greatest amount of variation while the elbow exhibits the least.

Summary

With this overview of the literature, I show that, while researchers have pursued an understanding of joint variation and the association between morphology and function, the results of this research remain inconclusive. Biomechanical loading shapes the joint surfaces throughout ontogeny via differential hydrostatic pressure. Joints arrive at their adult morphology through a process predominantly characterized by changes in shape. External surfaces of adult epiphyses retain their complex shape once established, and this substantial divergence from the columnar structure of the diaphyses often excludes them from research focused on long bone variation. When articular surfaces are considered, joints are often analyzed in isolation, or their variation is quantified using linear metrics that may be inappropriate for understanding the

morphological complexity of the epiphyses. Studies that do take a shape-based approach to epiphyses have indicated important functional or developmental relationships, yet questions remain unanswered regarding these relationships in modern humans, a unique case where the upper and lower limbs exhibit distinct functional and loading environments. The studies I present in Chapters II through IV use a shape-based analytical approach on the major limb joints to examine the relationship between variation, morphology, and conformity of human joint surfaces using function, loading, and soft tissue considerations as informative frameworks.

Research Questions and Dissertation Organization

This dissertation consists of three manuscripts, each exploring a different directive related to human joint shape: variation, covariation, and dysfunction. Below are the broad questions and associated expectations for each paper:

1. *How is morphological variation apportioned across the limb joints and articular surfaces of the human skeleton? Does the magnitude and apportionment of morphological variation reflect what we would expect based on its functional role? (Chapter II)*

Expectation: I predict that greater range of motion will limit morphological variation due to the plurality of functional demands being placed upon the joint, and that directly articulating surfaces will exhibit comparable morphological variance in shape due to shared function.

2. *How does morphological variation coordinate across the skeleton? How does covariance between directly articulating surfaces compare to covariance between surfaces that are analogous for function? (Chapter III)*

Expectation: I predict that directly articulating surfaces will exhibit high covariance due to their need to semi-conform for proper joint functioning, but that this covariance will be reduced in joints that are known to contain a greater amount of articular cartilage. I expect that there will be covariance between the functionally analogous joint shapes, but that this relationship will be weaker than between directly articulating morphologies.

3. *Are there shape qualities of the distal femur that are associated with the need for a total knee replacement? (Chapter IV)*

Expectation: I expect that distal femora of individuals who received a knee replacement will exhibit articular shape differences from individuals who never received a replacement, possibly suggesting innate joint qualities that predispose certain members of the population to joint disease and degeneration.

Following the three manuscripts, I will return in Chapter V to the broader context reviewed in this chapter to synthesize the key findings presented in each manuscript. Broader implications for the findings will be discussed as they relate to the literature presented here, along with a discussion of related future research endeavors.

Materials Overview

I provide specific information about samples, measurement methods, and analytical approaches in Chapters II, III, and IV. However, it is useful to provide an overview of the sample I used and the logic behind data collection for the fuller study. For these reasons, I provide detail about sampling and data collection methods below.

Why humans?

While understanding broad patterns of joint morphology across vertebrate taxa would no doubt be informative for understanding the effects of different locomotor regimes, postures, and limb function on joint morphology, the present study aims to establish intraspecific morphological variation using modern humans as a unique case study. With the most divergent upper and lower limbs of any primate, a human sample creates an opportunity for comparing homologous joint morphologies that experience entirely distinct biomechanical environments. The chosen skeletal collection (described below) has a rich archive of imaging and ancillary biodata and allows for a large sample size that would not otherwise be achievable with most non-human primate collections. The results of this focused, intraspecific analysis of joint shape will lay the groundwork for future studies that compare among vertebrate taxa by establishing the patterns of variation and trait interrelatedness that can exist within a species, patterns that will inevitably drive the relationships observed among species.

Joints of Interest

The joints selected for Chapters II & III consist of the glenohumeral shoulder, the humeroulnar elbow, the acetabulofemoral hip, and the tibiofemoral knee. These joints allow for representation of both girdle and limb bone elements and provide functional analogs for comparison in the opposing limb. For example, the inclusion of both the shoulder and hip allow for comparisons to be made between the high range of motion ball-and-socket joints in both limbs. The functional divergence of the human limbs at large allows for the observation of possible differences due to functional analogs being load-bearing (e.g., the hip) vs. non-load bearing (e.g., the shoulder). Each joint and articular surface are also serially homologous with their functional analog in the opposing limb, meaning their development is linked by shared

growth factors; the exception to this is the proximal ulna–proximal tibia pairing that are analogous for function but *not* serially homologous. This provides an opportunity to assess the effects of shared function on joint shape covariance in the absence of underlying developmental relatedness (see Schmidt and Fischer, 2009). The true serial homolog to the ulna is the fibula, however the fibula was excluded from the present study due to its lack of direct interaction with the main articulation of the knee. In the forearm, the ulna was chosen in favor of the radius due to its greater shared surface area with the distal humerus that presumably relates to the degree of influence these elbow morphologies exert on one another.

Sample – Chapters II & III

The Bass Donated Skeletal Collection housed in the Department of Anthropology at the University of Tennessee, Knoxville is one of the most well-documented modern human skeletal collections, containing upwards of 1,800 accessioned skeletons. A major asset of the collection is its archive of antemortem data that accompanies each body donor. Through this comprehensive archive, there is access to self-reported demographic categories (age, sex, ancestry), biological data (e.g., stature, weight), medical data (e.g., surgical interventions, disease history) and activity-related information (e.g., lifelong occupation and habitual activities). With the Bass Collection annually accepting body donations from across the country, it constitutes a broad modern sample ideal for investigating questions of human variation. Further, each body donor to the collection undergoes natural decomposition in a controlled environment, yielding a degree of skeletal completeness and bone quality unmatched by most archaeological, forensic, or comparative collections. Given that this study aims to understand articular surface morphology of contemporary humans, the Bass Collection forms the most appropriate sample.

The Bass Collection houses a repository of computed tomography (CT) scans taken for 820 of the currently accessioned skeletons. Scans were conducted postmortem and post-decomposition and therefore reflect only the skeletal remains of each body donor. Chapters II & III of this dissertation utilize a 200-individual subset of the 820 total body donors with associated CT scans. The 200-individual sample size is the result of various criteria needed for the study; the sample criteria are as follows:

A.) An individual must have all six skeletal elements of interest (at least partially) present.

These elements consist of the left and right antimeres of the scapula, humerus, ulna, os coxa, femur, and tibia.

B.) Skeletal elements of interest must have completely intact articular surfaces. Articular surfaces consist of the glenoid fossa of the scapula, the humeral head and trochlea/capitulum of the humerus, the acetabulum of the os coxa, the femoral head and femoral condyles, and the tibial condyles.

C.) Articular surfaces should exhibit no visible pathologies or apparent joint degeneration (e.g., osteoarthritis, eburnation, lipping, exposure of trabecular bone).

D.) Articular surfaces should exhibit no medical intervention (e.g., joint replacement hardware or other restorative implements).

Individuals not meeting these criteria were excluded from the sample. Due to the overall fewer number of females with associated CT scans and the increased prevalence of bone density loss that made segmenting female limb bones more difficult, the total number of female individuals meeting the above criteria ($n = 84$) were used to dictate total sample size; the final sample size for male individuals ($n = 116$) was intended to bring the total sample size to an appropriate

amount for carrying out the proposed analyses, but not to exceed the female sample size by so much that the effects of sex could not be reliably analyzed.

The skeletal CT scans (details about which may be found in Chapter II) allow for the creation of three-dimensional (3D) surface models using autosegmentation code in Matlab; surfaces were hand-segmented as-needed in Avizo. Surface models were imported into Stratovan Checkpoint for the collection of 3D landmark coordinates and contour data on the sixteen joint surfaces per individual. A total of 83 landmarks and 19 semilandmark curves were placed on each skeleton in the sample, which produces a total of 16,600 landmarks and 3,800 curves on the final sample of 200 individuals. With the exception of novel landmarks on the scapula, the landmarks for the remaining bones are modified from Arias-Martorell, Tallman, Potau, Bello-Hellegouarch, and Perez-Perez (2015), San Millán, Kaliontzopoulou, Rissech, and Turbón (2015), Tallman (2013, 2016); novel contours are defined (Tables II.4 – II.9) for the present study by the author HH. Figures II.1 – II.6 demonstrate landmark placement. Note that only left side bones are displayed in these figures but landmark data is collected bilaterally. All landmark data are selected to represent the shape of each joint as well as major articular contours that display complex topography. I undertook a calibration period to ensure the clarity of landmark locations and consistency in landmark placement. A two-sample *t*-test conducted on two trials of a sample of four individuals confirmed no significant differences in landmark placement between trials ($p > 0.05$). After landmarks were collected on the full sample, coordinates were exported to Excel spreadsheets for statistical analysis in RStudio.

The sample is intended to capture a range of body sizes, ages, and activity levels. Though direct observation of investing joint ligaments and cartilages are not achievable through dry bone

data, the varying degrees of soft tissue known to be present at each joint will be considered in the contextualization of hypotheses and results in Chapters II & III.

Sample – Chapter IV

The sample for Chapter IV was also derived from the Bass Donated Skeletal Collection, but did not employ 3D segmentation from the CT scan database. Given Chapter IV's focus on clinical application, the sample consists of two sample groups: 12 individuals that received unilateral total knee arthroplasty (TKA) during life, and an additional 35 who received no knee replacement as a comparative sample. The selection criteria for the sample were as follows:

A.) TKA sample

- a. Skeleton must exhibit TKA hardware on only one knee (either left or right).
- b. The opposite, non-TKA knee must be free from visible pathologies or apparent joint degeneration (e.g., osteoarthritis, eburnation, lipping, exposure of trabecular bone).

B.) Non-TKA sample

- a. Skeletons must exhibit no TKA hardware or other medical intervention at the knee.
- b. Skeletons must be free from visible pathologies or apparent joint degeneration (e.g., osteoarthritis, eburnation, lipping, exposure of trabecular bone).
- c. Sex and age for each control individual should match sex and age of at least one of the TKA individuals.

Each TKA individual has at least two corresponding non-TKA individuals that serve as a direct match for sex and age. This ensures that comparisons control for some of the demographic factors that are most influential to an individual's size, shape, and bone quality.

Fourteen three-dimensional landmarks were collected on both the left and right distal femora of the non-TKA sample, where possible; for the TKA sample, landmarks were collected on the knee without replacement hardware (landmark definitions in Table III.3 and demonstrated in Figure III.1). Landmarks were collected directly on the distal femora using a Microscribe. The Microscribe was positioned on a lab bench and was not moved for the duration of data collection. Femora were affixed in a standard position relative to the Microscribe using clamps. Coordinates collected with the Microscribe immediately populate an Excel spreadsheet that was later imported to RStudio for statistical analyses.

Significance of Research

The current lack of understanding of morphological structure among human joint surfaces impedes a holistic picture of variation that is relevant to a variety of academic and applied fields. As noted earlier, a growing literature has demonstrated the importance of understanding how multiple aspects of the skeleton influence variation in one another, both developmentally and functionally. Epiphyses have been generally studied in isolation, or as a singular articulating joint surface, with the assumption that the opposite articular surface will correspond equally; the design of this dissertation directly tests that assumption, among others.

A central merit of the studies contained herein is their potential to add to the developing literature about the independence and covariance of traits, which has significant influence on the developmental and evolutionary models for those traits. By showing the degree to which joint shapes are non-independent, this research affects future studies on the evolution of human limbs. Likewise, additional to the main findings of this research, this dissertation will evaluate the

current epistemological approach to the complexity of epiphyses, which often takes the form of size quantification to the exclusion of shape. This study addresses these shortcomings through comprehensive shape analysis and creative statistical solutions designed to capture and compare unique epiphyseal variation and, by exploring questions of functional morphology and trait relatedness for an under-studied region of the skeleton, will contribute to a more holistic understanding of human variation and morphology.

Populational shape analysis of joint morphology has interdisciplinary application. Within biological anthropology alone, understanding joint shape holds meaning for studies of locomotion and the evolution of bipedalism; forensic anthropological methods concerned with rearticulating comingled skeletal remains; and paleoanthropological efforts to classify attributes of fossil hominins from joint size, shape, and orientation. Evolutionary biologists also endeavor to identify phenotypic trait interactions that will solidify evolutionary models. But the largest stakeholder in joint research comes from the clinical sector where osteoarthritis is the leading joint disease, often resulting in treatment via total joint replacement. With arthritis prevalence only increasing in future decades, joint health is a top priority for healthcare practitioners. Through a nuanced understanding of joint shape and how shape relates to replacement status, it may become possible in the future to predict which individuals in a population are predisposed to joint disease based on their joint morphology.

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CHAPTER II: THE APPORTIONMENT OF MORPHOLOGICAL VARIANCE IN HUMAN LIMB SYNOVIAL JOINT ARTICULAR SURFACES

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Auerbach as:

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This chapter constitutes novel research and regularly uses pronouns “we” and “our” to refer to the collective contributions of the co-authors. It should be noted, however, that in addition to conducting the majority of the research including data collection and analyses, I, Haley Horbaly, am the author in the ordinary sense.

Abstract

Objectives: Synovial joints in human limbs strike a balance between mobility, stability, and articular fit, yet little is known about how these conflicting demands pattern intraspecific variation in articular shape. In this study, we use geometric morphometrics to establish the apportionment and magnitude of morphological variance in articular surfaces of the human shoulder, elbow, hip, and knee. We hypothesize that variances will be comparable between articulating surfaces within a joint and will be larger in joints with greater ranges of motion.

Methods: Three-dimensional landmarks were taken on the articular surfaces of the glenohumeral, humeroulnar, acetabulofemoral, and tibiofemoral joints from CT scans of 200 skeletons from the Bass Donated Skeletal Collection (84 females, 116 males). Root mean-squared distances between articulations calculated from Procrustes shape coordinates were used to determine variance distributions.

Results: We found no difference in variances for each articular surface between the sexes or between left and right articular surfaces. A high range of motion is associated with greater morphological variance; however, this pattern is largely driven by the concave articular surfaces of each joint which consistently exhibit significantly greater variance than their convex counterparts.

Discussion: This striking pattern of differential variance between articulating morphologies points to potential disparities in development between them, and opportunities for suboptimal shape matches. Consistently high variance in concave surfaces may relate to chondral modeling theory for the formation of joints. Establishing intraspecific morphological variance patterns is a first step in understanding coordinated evolution among articular features.

Introduction

Decades of study have established that primate limb joint morphology reflects range of motion (excursion) required for function and locomotion while also accommodating sometimes antagonistic demands of joint stability and articular fit (Hamrick, 1996a, 1996b; Martelli & Pinskerova, 2002; Ruff, 1988; Ruff & Runestad, 1992; San Millán, Kaliontzopoulou, Rissech, & Turbón, 2015; Tallman, 2013, 2016; Yapuncich & Granatosky, 2021). Additionally, articulations must accommodate forces transmitted across the joint, and thus articular size generally scales with body size, though this relationship varies among taxa (Jungers, 1991; Lague, 2003; Ruff, 1988, 2003). To meet these requirements, joint morphology develops through stereotypical growth patterns that produce conformity of articulating surfaces, though differences between limb function and developmental timing may introduce variation across distinct joints. Human

limbs exemplify one of the greatest divergences of function among primates (Rolian, 2009; Young, Wagner, & Hallgrímsson, 2010), though, like all tetrapods, development unfolds with similar, conserved processes in both the upper and lower limb (McQueen & Towers, 2020; Tickle, 2015; Towers & Tickle, 2009).

Variance in the morphology of skeletal elements reflects a combination of factors, including genetic and environmental sources, as well as their interaction over the course of growth and development (Kappen, Neubüser, Balling, & Finnell, 2007). While establishing the sources of variance is difficult given the nonlinear effects of developmental processes (Hallgrímsson et al., 2009), such processes ultimately control the amount of morphological variation expressed. This is because development occurs along specified trajectories that limit morphological outcomes (Salazar-Ciudad, 2021), and so variation in a trait reflects underlying genetic variance (Cheverud, 1988; Sodini, Kemper, Wray, & Trzaskowski, 2018). While a developmental model is beyond the scope of this study, the relevance of both development and functional roles to the outcome of joint shape complexities makes the study of variance in adult morphology useful toward establishing testable hypotheses about those roles.

Thus, given the importance of joint shape for function, locomotion, and other activities, this study uses three-dimensional geometric morphometrics to establish the apportionment and magnitude of shape variance in the human shoulder, elbow, hip, and knee. We hypothesize that variation within joints between directly articulating surfaces should not differ, reflecting underlying processes of targeted growth and development which ensure these surfaces are complementary for function. Relative morphological variation among joints, however, may differ given the differences in development, loading contexts, and functional anatomies of the shoulder, elbow, hip, and knee.

By contextualizing these patterns of variation with joint properties such as function, range of motion, and soft tissue presence, this study examines potential factors that may relate to sources of variance in joint morphology. Understanding such morphological trait variation is a foundational step toward better understanding the relationship between evolution and development in shaping morphology (Agosto & Auerbach, 2021b, in press; Roseman & Auerbach, 2015; Savell, Auerbach, & Roseman, 2016).

Context for Understanding Sources of Joint Morphological Variance

Understanding external articular morphology's responsiveness to activity and loading, both during development and after maturation, is essential when considering sources of variation in joint morphology. The precise mechanisms of joint morphogenesis remain elusive, but researchers have suggested that a combination of biochemical and mechanical inputs are responsible for the morphological complexities of the adult joint (Carter & Wong, 1988; Chijimatsu & Saito, 2019; Frost, 1979; Hamrick, 1999; Plochocki, Ward, & Smith, 2009; Rolfe, Shea, Singh, Bandyopadhyay, & Murphy, 2018; Zhou, 2021). Indeed, the main adaptive trajectories experienced by the joint surfaces may be best explained by chondral modeling theory (Frost, 1979; Hamrick, 1999). Chondral modeling argues that varying degrees of hydrostatic pressure within the joint capsule will shape the cartilage anlage so that at all points during development the opposing articular surfaces remain semi-congruent to one another in a way that maintains functional integrity of the joint. Specifically, portions of the joint surface that experience hydrostatic pressures between 1 and 10 MPa will experience chondrocyte proliferation and ossification resulting in a local expansion of the articulation; loads above or below this range will inhibit articular growth (Hamrick, 1999; Takahashi et al., 1997). Over time,

this growth model produces patterns of increasing joint surface congruence (Plochocki et al., 2009).

Given the chondral modeling framework, we may consider two studies that sought to assess functional adaptation in articular cortical dimensions but arrived at distinct conclusions regarding the ability of the external shape of epiphyses to reflect activity. Lieberman, Devlin, and Pearson (2001) and Plochocki (2004) analyzed articular differences between active and sedentary groups, with Lieberman et al. looking at sheep subjected to loading regimes of varying intensity, and Plochocki comparing human athletes to non-athletes. Lieberman et al. (2001) found no significant articular differences between sheep subjected to repeated exercise and sheep not treated with exercise, and this finding is regarded as strong evidence for low responsiveness or high restriction in articular surface cortical morphology to loading. Conversely, Plochocki (2004) found human articular variation to mimic side-biased patterns that are well-established for limb bone diaphyses (Auerbach & Ruff, 2004; Ingelmark, 1974; Ruff & Jones, 1981; Sakaue, 1998; Schultz, 1937; Trinkaus, Churchill, & Ruff, 1994), which implies that lateralized behaviors may exert influence on both epiphyses and diaphyses, as well as argues against the low response observed in the experimental sheep. Research design differences—including the use of quadrupeds versus bipeds, the nature of the exercise used in each study, and the possibility for longer-term asymmetric loading in humans—could have contributed to the apparent contradictions in study conclusions. Given that humans exhibit side-biased activity associated with handedness that is enculturated from a young age (Blackburn, 2011; Shaw, 2011; Steele & Mays, 1995), it is possible that humans already have a greater propensity for articular differences than quadrupedal sheep whose limbs experience more evenly dispersed locomotor activity.

It should be emphasized as well that both Lieberman et al. (2001) and Plochocki (2004) quantified articular variation using linear dimensions; however, developing joint surfaces, which transform and elaborate as humans engage in different movement behaviors over the course of primary growth, are perhaps better characterized by changes in shape rather than size (Plochocki et al., 2009). Nevertheless, studies have predominantly utilized linear dimensions of epiphyses or articular surfaces to explore questions about joint responses to loading, scaling with body size, or functional relationships with movement in joint morphology. The use of linear dimensions, however, restricts the detection of joint variation to patterns of size and misses potentially pertinent variation introduced by shape (Jungers, Falsetti, & Wall, 1995). Thus, while the study of dimensions of joint size is warranted when investigating scaling relationships, shape analysis provides opportunities to examine nuanced associations with function and mechanics.

Studies that take a shape-based approach to joint articulations have identified links between specific articular shape properties and discrete kinematic movements (Martelli & Pinskerova, 2002; Sylvester, 2015). These studies focused on joint contours, demonstrating that they exhibit functional signatures indicative of the joint's range of motion (Martelli & Pinskerova, 2002) or biomechanical environment (Sylvester, 2015). Martelli and Pinskerova (2002) found that human cadaver knees exhibit clear differences in morphology between the portions of the articular surface in contact from zero to twenty degrees (full extension to slight flexion) and twenty to 120 degrees (slight to full flexion). Sylvester (2015) explored whether the chondral modeling theory (Frost, 1979; Hamrick, 1999) can explain quadruped condylar morphology and identified varying radii of curvature to correspond to the ground reaction forces experienced during locomotion; specifically, peak forces align with larger condylar radii (less curved, flatter surfaces). While epiphyseal remodeling during an individual's lifetime primarily

affects change in trabeculae, the work by Martelli and Pinskerova (2002) and Sylvester (2015) show various portions of articular surface shape is modeled according to its role in range of motion.

Other research has focused on locomotor signatures between groups, rather than within individuals or groups. Tallman (2013), for example, established that the degree of covariance between upper and lower limb epiphyses in non-human primates and fossil hominins has a close association with the species' respective intermembral indices. Intermembral indices are associated with broad locomotor groups among primates (among other mammals; see Granatosky, 2018), and so these results indicate that epiphyseal covariance is an indicator of locomotor repertoire. Yapuncich and Granatosky (2021) focused on ankle joints of lorises and cheirogaleids, as the former have more joint mobility at the subtalar joint. They found that lorises exhibit a reduction in articular surface congruence and a more distinctly saddle-shaped talar facet. These and other studies further reinforce the ability to detect nuances of kinematics and locomotion through the study of joint shape, yet joint shape remains largely unexplored within humans despite extreme limb functional divergence and low integration (Rölian, 2009; Young et al., 2010).

Within the context above, here we investigate the relationship between variation, morphology, and conformity of human joint surfaces using joint function and anatomical considerations as informative frameworks. As outlined above, it is expected that the magnitudes of variance will be similar between corresponding articular surfaces, given their interrelated growth and shared functional context. In addition, we expect that joints with smaller excursions will exhibit increased variation in shape. Of the joints under study, we can broadly organize them on a scale from higher range of motion joints (shoulder, hip) to lower range of motion joints

(elbow, knee) using commonly accepted reference values for range of motion (Barnes, Van Steyn, & Fischer, 2001; Soucie et al., 2011; American Academy of Orthopaedic Surgeons, 1965; Zarins, Rowe, Harris, & Watkins, 1983). Theoretically, the requirement of fulfilling multiple functional demands (e.g., those joints with a higher range of motion) will promote morphological restriction, whereas joints that perform a smaller range of motion might have more leeway for shape variation. Given this, we expect to observe less morphological variance in the shoulder and hip, given their plurality of functional demands. To distinguish relative mobility, we have separated the ranges of motion into four quartiles of 45 degrees each (e.g., 0-45, 45-90, 90-135, and 135-180 degrees as equating to low, medium-low, medium-high, and high range of motion quartiles). Table I.1 outlines these quartiles and the range of motion available at each joint. Finally, we hypothesize that there will be no significant differences in variance between sides of the body or between sex groups. While males and females are known to exhibit differences in carrying angle of the elbow and quadriceps angle of the knee (Kothapalli, Murudkar, & Seerla, 2013; Mahmood, Goel, Grover, & Bedi, 2016; Purkait & Chandra, 2004; Ruparelia, Patel, Zalawadia, Shah, & Patel, 2010), we expect that dimorphism is a product of differences in the size and orientation of articulations and not the overall shape.

Materials and Methods

Sample

Given the emphasis of this study on modern human joint morphology, the skeletal sample was selected from the William M. Bass Donated Skeletal Collection. The Bass Donated Collection is a modern skeletal collection comprised of willed body donors to the University of Tennessee's Forensic Anthropology Center. This collection includes a database of computed-

tomography (CT) scans taken for 820 of the skeletons accessioned into the collection. These scans consist of isotropic voxels of 0.625mm^3 and were conducted as part of collaborative research projects (e.g., Shirley, Wilson, & Jantz, 2011; Sylvester, Merkl, & Mahfouz, 2008).

Skeletons were included in the present study based on criteria to ensure completeness and nonpathological anatomy. First, a skeleton must have had all six skeletal elements of interest (at least partially) present: the left and right scapula, humerus, ulna, os coxa, femur, and tibia. Second, skeletal elements of interest must have had completely intact articular surfaces: the glenoid fossa of the scapula, the humeral head and trochlea/capitulum of the humerus, the acetabulum of the os coxa, the femoral head and femoral condyles, and the tibial condyles. Finally, articular surfaces exhibited no visible pathologies or apparent joint degeneration (e.g., osteoarthritis, eburnation, lipping, exposure of trabecular bone), as well as no medical intervention or arthroplasty (e.g., joint replacement hardware or other restorative implements).

Individuals not meeting these criteria were excluded from the sample. Due to the overall fewer number of females with associated CT scans and the increased prevalence of bone density loss that made segmenting female limb bones difficult, the total number of female skeletons meeting the above criteria ($n = 84$) were used to dictate total sample size; the final sample size for male skeletons ($n = 116$) was intended to bring the total sample size to an appropriate amount for carrying out the proposed analyses, but not to exceed the female sample size by so much that the effects of sex could not be reliably analyzed. The total resulting sample size for the present study consisted of 200 skeletons.

As the sample was scanned after bone was defleshed, joint-related cartilages, including labra and menisci, were not preserved. However, dry bone joint surface morphology reflects variation in shape (Martelli & Pinskerova, 2002; Sylvester, 2015) and also provides homologous

morphometric landmarks that reflect biological variation alone, while articular cartilages in donors may be affected by differential wear, degenerative processes, and other sources of variation that are not under investigation in this study. This noted, we will consider prior studies that have focused on cartilage in the contextualization of observed variation in the present study.

Joints under Study

We investigated variation within the shoulder (glenohumeral joint), elbow (humeroulnar joint), hip (acetabulofemoral joint), and knee (tibiofemoral joint). These synovial joints were selected over other joints of the human skeleton due to their high degree of excursion, precedent for their study (e.g., Lieberman et al., 2001; Plochocki, 2004; Tallman, 2013), and reflection of general limb movement and activity. Furthermore, the joints of interest represent upper and lower limb homologues allowing for comparisons between joints that have similar types of movement (e.g., the shoulder and hip) but routinely experience different biomechanical demands due to limb functional divergence, namely due to locomotion.

As outlined below, three-dimensional morphometric landmarks were chosen to represent the articular surfaces of these joints. Landmarks that reflect ligament and tendon insertions, such as the intertrochlear ridge of the femur or epicondyles of the tibia, were not included. This is because we sought to narrowly examine variance among the articulations of limb bone joints without wanting to add confounding variation arising from periarticular dimensions, and which have a different response to loading than the bone of synovial joint surfaces. We note this in part because some prior studies that have examined articular dimensions included landmarks or linear measurements incorporating periarticular anatomy.

Data Collection

Three-dimensional landmark data were collected by HH from whole bone surface models of 200 skeletonized body donors from the Bass Donated Collection. Surface models were created from CT scans either through hand-segmentation in Avizo 2021.1 or autosegmentation in Matlab 2021b; autosegmentation was achieved using custom script by ADS. Surface meshes were exported, and landmarks were then placed on the surface models in Stratovan Checkpoint. Landmark illustrations for each articular surface are included in Figures I.1 – I.6; definitions are included in supplementary information Tables I.4 – I.9. Though figures I.1 – I.6 depict landmarks on left side elements, all landmarks were collected bilaterally, resulting in 150 landmarks per individual. Because articular surfaces are irregular compared with other bony anatomy used in geometric morphometrics, landmarks were chosen that occurred at extreme points along a surface (e.g., the conoid process, the superior point of the glenoid fossa), while semilandmark contours were chosen to connect two of these extrema and capture articular surface topography. To assess landmark definitions and intraobserver error, HH conducted repeated landmark placement trials on four individuals, amounting to 600 landmarks. Trials were conducted a week apart. Raw landmark coordinates for the intraobserver trials were subjected to a Generalized Procrustes Analysis, and associated plots indicated high intraobserver agreement on landmark placement between trials. Consistency between trials was confirmed through paired t-tests for each skeleton ($p > 0.05$ for all trials for all bones).

Statistical analysis

All analyses of landmark data were performed in R (R Core Team, 2021). Prior to analysis, landmarks were subjected to full Procrustes transformation for each joint using the ‘geomorph’ package (Adams, Collyer, Kaliontzopoulou, & Baken, 2021; Baken, Collyer,

Kaliontzopoulou, & Adams, 2021). Right and left sides were transformed separately, as were females and males.

Variances for each articulation (e.g., the humeral head, the glenoid fossa, the distal humerus, etc.) and for each joint (e.g., both the humeral head and glenoid fossa together) were determined by generating variance-covariance (VCV) matrices of Procrustes shape coordinates. As covariance of landmarks was not under study in this investigation, off-diagonal elements of the VCV matrix were ignored. The trace (summed variance) of the VCV matrix was used to directly compare variance in an articular surface or whole joint between males and females, as well as between antimeres of the surface or joint. The trace difference between males and females were calculated, then compared to 1,000 randomly permuted trace differences drawn from the pooled sex sample. The actual trace difference between sexes was then compared to the average permuted difference to determine statistical significance. Given the quantity of comparisons conducted, we chose a critical alpha of 0.01 to be statistically conservative.

Direct comparison of shape variance can only occur between objects with homologous landmarks. Because the landmarks from each articular surface are inherently non-homologous, their trace values cannot be directly compared. To address this, a distribution of the root mean square distances (RMSD) for each articular surface was produced between individuals. Distributions were created by calculating the RMSD values between the corresponding articular landmarks of two individuals, repeating this process for all pairwise combinations of individuals in the sample. The resulting RMSD values serve to approximate how similar (lower RMSD values) or dissimilar (higher RMSD values) two individuals are at a given articular surface. This yields a distribution of 19,900 RMSD values for the sample, acting as a landmark-free approximation of articular shape variance. This process was repeated to create separate RMSD

distributions for each articulation, which can then be compared to assess relative differences in sample variance among articular surfaces. Distributions were compared using Kolmogorov-Smirnov tests with a critical alpha of 0.05.

Results

Trace permutations were used to test for antimeric and for sex differences in each joint and articular surface, and results are reported in Tables I.2 and I.3. No significant differences in variance were observed in trace values between left and right joints or identical left and right individual articular surfaces ($p > 0.01$ for all joints, articulations) (Table I.2). While no differences in variance were observed between sides, comparisons between sides were further examined in the analysis of sex differences in variance in case there is a latent interaction between side asymmetry and sex. No significant differences ($p > 0.01$) are observed in joint or articular surface variances between males and females (see Table I.3). We note that there are slightly greater differences in variance observed in the left side than the right side between the sexes, though as shown in Table I.2 there is no significant side difference in either joints or articular surfaces. Given these results, we explored differences in variation between joints and articular surfaces using left side measurements and combined sexes in all further analyses.

Joint variance was compared using a RMSD analysis. Violin plots demonstrate the RMSD distributions for each joint (Figure I.7) and each surface (Figure I.8). Higher values indicate greater differences among individuals, and thus more variance within the sample. Both the elbow and knee joints in their entirety have less variation than the shoulder and hip joints. The greatest variance among articular surfaces is found in the acetabulum, and collectively the joint surfaces that are convex (i.e., humeral head, distal humerus, femoral head, and femoral

condyles) have significantly less variation ($p < 0.05$) than concave articular surfaces (i.e., glenoid fossa, proximal ulna, acetabulum, and tibial condyles). Post-hoc Kolmogorov-Smirnov tests indicate significant differences between all pairs of joint and articular variance distributions ($p < 0.01$ for all pairs). From this we conclude that the greater variance observed in the shoulder and hip is driven by the greater variance in their respective concave articular surfaces.

Discussion

Our study demonstrates novel findings about morphological variation within and among the major limb joints of human limbs. In general, both overall joint morphology and the morphology of constituent articular surfaces are remarkably consistent between sides of the body and between females and males. As reviewed in more detail below, the relationship between joint excursion and shape variance broadly indicates that those with larger ranges of motion have more variance, a finding inconsistent with our expectations based on the functional demands of each joint. Surprisingly, our results do not support similar amounts of variance between articulating surfaces within joints, but rather an unprecedented finding of systemic differences in variance apportionment between concave and convex articular surfaces.

Sidedness and Sex Effects on Joint Variation

There were no significant results among the comparisons of traces within articulations between sides and among sexes. This result suggests that, while there are documented patterns of directional asymmetry in articular size (Auerbach & Ruff, 2006; Plochocki, 2004), the apportionment of variance in the shape of the same articulations is maintained regardless of asymmetry within individuals or between the sexes. This indicates that over the course of development and growth, the same articulations are subject to similar restrictions or lability in

their response to perturbations or environmental effects, namely mechanical effects of loading. The significance of this conclusion with respect to sensitivity to factors that could contribute to variance will require additional study; without assessing the amount of variance present in the shape of other aspects of bone morphology (e.g., variance in cross-sectional geometric properties of diaphyses), the amount of variation indicated in our results lacks broader context.

Nonetheless, the consistency in variance within joints for the same surfaces does provide support the arguments made by multiple authors about limited responses to loading in articular shape (Auerbach & Ruff, 2006; Lazenby, Cooper, Angus, & Hallgrímsson, 2008; Lieberman et al., 2001; Ruff, 1994, 2002). Our results do not contradict studies that indicate changes in articular size in response to loading (e.g., Plochocki 2004), but the lack of significant difference in variances between sides suggests that directional asymmetry would result in a complete shift of the variance around a mean in cases of asymmetry within joints. Though Auerbach and Ruff (2006) did not examine differences in the dispersion of asymmetry between sides, a visual examination of their Figure I.1 does not suggest notable differences in the distributions of asymmetry between sides for articular dimensions. We therefore conclude that our results do not contradict evidence that most adaptive responses within epiphyses occur in trabecular bone and not the cortical shape, and if cortical shape is affected by environmental or other sources of variation the impact neither increases nor decreases the morphological shape variance among human joints.

Biased Apportionment of Variance between Joint Convex and Concave Surfaces

While the amount of variation is consistent within each articulation with respect to side and sex, variances significantly differ between joint articular surfaces. Comparisons among whole joints requires further consideration, but attention prevails on the apportionment of

variance within joints. All the joints we examine have one concave and one convex surface, as is the case in almost all human synovial joints. The apparent presence of relative constraint in variation on convex joint morphology in each of the major limb joints is perhaps indicative of developmental processes, whereby concave components undergo a modeling trajectory more likely to generate variance in shape.

As we review in the Introduction, under chondral modeling theory (Carter & Wong, 1988; Hamrick, 1999; Plochocki et al., 2009) hydrostatic pressure on chondral anlagen and articular cartilage affects the amount of growth inhibition that occurs at a joint. Support for chondral modeling theory is mixed (see Congdon, Hammond, & Ravosa, 2012; Hammond, Ning, Ward, & Ravosa, 2010; Martelli & Pinskerova, 2002; Sylvester, 2015). Yet, if chondral modeling theory applies to our results, then one of two possible conclusions can be drawn: 1) differential pressure magnitudes act on the convex and concave surfaces, resulting in differential growth and accrued variance between them, or 2) pressure magnitudes are equal between the convex and concave joint components, but they experience differential ability to respond to the pressure via chondral modeling. Given that any force (whether it be hydrostatic, biomechanical, or otherwise) transmitting between two articulating objects will result in equal and opposite pressures on each surface, it is unlikely that the first scenario is true—convex and concave joint components are likely not experiencing different forces. It is much more likely that, as part of the same joint capsule, both articulations are experiencing the same magnitudes of hydrostatic pressure, yet the convex surface is more limited in its ability to respond via chondral modeling compared to the concave surface. This points to a possible model of joint formation whereby the convex surface is more inflexible to external pressures due to its underlying genetics, and thus leads the formation of the joint; the concave surface, then, must exhibit greater flexibility to

accommodate for the more restricted convex component, and hence shows an enhanced ability to respond via chondral modeling as well as greater variation in the definitive concave surface.

Because joint morphogenesis is one of the least understood aspects of embryonic development (Kan et al., 2013; Pacifici, Koyama, & Iwamoto, 2005; Pacifici et al., 2006; Zhang et al., 2020), there is currently little explanation for differential morphogenesis of the convex and concave articulations. In their study conducted on interphalangeal joint formation in chick embryos, Pacifici et al. (2005) noted that GDF5, a growth factor responsible for establishing and maintaining the future joint site and structures within the developing cartilage anlage, becomes heavily concentrated on the convex surface after the onset of morphogenesis and yet is undetectable on the surface of the concave component. Only GDF5 is found to have a high concentration to the developing convex articular surface, while Gli-3 and others maintain relatively even distribution throughout the interzone. The entirety of GDF5's role in morphogenesis is still unknown, but it is possible that this biased concentration of GDF5 transcripts during development may be indicative of a broader divergence in growth trajectories for the convex and concave joint components, and this possibility should be explored in future developmental studies. Some research has already demonstrated that more robust developmental networks produce less phenotypic variance in a population given their reduced sensitivity to perturbations (Sears, 2014), making it possible that a highly robust network—of which GDF5 is only one part—is responsible for morphogenesis of the convex components of joint articulations. Conversely, the absence of GDF5 on the concave joint surface as described by Pacifici et al. (2005) may indicate the presence of a different, less robust morphogenic network that may initiate a sequence of accrued variation in subsequent stages of development (Hallgrímsson et al., 2009).

While our results give confidence that the pattern of variance apportionment between concave and convex surfaces within joints is a robust result, we note that the greatest variance is in the two concave joint surfaces that are part of “ball-and-socket” joints. It is possible that some of the additional variance for the acetabulum and glenoid fossa are reflections of greater flexibility permitted by articular cartilage structures. That is, these joint surfaces may be able to vary more because articular cartilages reduce the effects of that morphological variation on conformity with the heads of the humerus or femur. Though joint cartilage could not be directly incorporated into this study due to the nature of a fully skeletonized sample, it is important for contextualizing results and is a contributing factor for the patterns of variance observed here. Articular cartilage exists to varying degrees in each joint and, in addition to reducing friction and absorbing and distributing the shock of locomotion, cartilage supplements the shape of the bony joint to enhance articular fit. In many of the joints most padded by cartilage, the cartilaginous component is anchored to the concave surface. The menisci of the knee attach to the margins of the tibial condyles, creating cup-like receptors for the femoral condyles. Similarly, the labrum of the shoulder originates on the margins of the scapular glenoid fossa, extending out to hold the humeral head in contact. Given the interrelated nature of the concave surface with the cartilage component, it is possible the partial accommodation of joint conformity by the cartilages relaxes the restrictions on the concave bony component resulting in the greater variance we see here. However, if this were the case, we would perhaps expect to see the greatest variance, then, in the proximal tibia, since it anchors the thickest and most elaborate joint cartilage (menisci) of the joints under study (Shepherd & Seedhom, 1999). Instead, the results of this study indicate that out of all the concave joint surfaces analyzed, the proximal tibia has the least variance of the group. Thus, the impact of cartilage on variance is a contributing factor in concave articular

shape morphology, but it should be considered alongside the potential inherent developmental differences discussed above.

Joint Variation and Movement

Within the specific context of variance among surfaces that comprise joints, the pattern of variance among whole joints unsurprisingly matches the pattern of variance in concave joint surfaces. Nevertheless, observed joint variance distributions run counter to the proposed hypothesis that joints exhibiting greater ranges of motion in more directions—the shoulder and the hip—would exhibit limited variance due to the multitude of movement requirements they must fill. Variance distributions demonstrate that the shoulder and hip show significantly more morphological variance than the elbow and knee. In context of the discussion above, it is possible that the differences in articular cartilage among the joints, which impacts joint excursion, could be a contributing factor to both the variance and its relationship with range of motion. That is, while there is low variance in the knee compared to the other joints, it is possible that there is missing morphological variation in that joint provided by the menisci, though it is equally possible that the menisci and articular cartilage further reduces variation in joint morphology. Without a direct measurement of the study sample's cartilage morphology, however, it remains unresolved what role articular cartilage would have in affecting the results reported herein on the ossified anatomy.

Higher variance in the articular morphology of the hip and shoulder has some functional implications. Unequal variances between articular surfaces means that the heads of the humerus and femur are morphologically more restricted, and so disconformities between bones in these joints would be the result of variation in the acetabulum and glenoid fossa. This may also implicate these concave surfaces as being a larger contributor to mechanical instability,

especially if the stability of articulations relates to a particular range of the total variance expressed in surface anatomy. One may predict that reduced mechanical stability relating to mismatches in the morphological distribution of concave surfaces relative to the more limited range expressed in their convex articulations could lead to articular disease (e.g., arthritis, eburnation, or cartilage trauma). This hypothesis is beyond the scope of this study, but would be useful to examine with respect to individuals who encounter joint pathologies, especially those that make them candidates for arthroplasty.

Which aspects of these articular surfaces are driving the overall ranges of variation observed in this study deserves further study as well. It is unlikely that all dimensions of a joint surface contribute equally to the overall variance reported. The nature of the approach we take in examining variance does not perfectly align with comparisons using Procrustes analysis, and so detection of which landmarks are driving the greater variation in some joint surfaces awaits future analysis.

Conclusion

Our study has revealed an unprecedented pattern of variation apportionment in the articular surfaces of limb bones. While reasons for high concave surface variation and their impact on movement await future studies, the patterns described herein have potentially important implications for developmental models of limb epiphyses and etiology for articular disease. Furthermore, our results add nuance to studies of asymmetry and of functional impacts on joint morphology, showing that, at least in our sample, if lateralized behaviors and directional asymmetry were present, then there was no impact on variation.

Our research thus lays groundwork for future studies. One tantalizing question is, by first identifying the scope of underlying variation in the joints of humans, whether the patterns reported here extend to other taxa, opening potential future comparative studies on primates and other vertebrates. In addition, by knowing how variation occurs in and is coordinated across traits, researchers are better able to determine which traits to examine in future studies of evolvability and integration. By comparing traits within joints as well as among articulations, our analysis contributes to a growing body of literature in the biological and evolutionary sciences that has focused on the organization of trait variation and covariation at the whole-organism level (Agosto & Auerbach, 2021a; Conaway, Schroeder, & von Cramon-Taubadel, 2018; Melo, Porto, Cheverud, & Marroig, 2016; Roseman & Auerbach, 2015; Savell, 2020; Savell et al., 2016; Sears, 2014).

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APPENDIX I

Table I.1: Joint ranges of motion, the values of which are commonly accepted reference values.* Degree values correspond to a range of motion category defined as quartiles of 45 degrees each (e.g., 0-45, 45-90, 90-135, and 135-180 degrees as equating to low, medium-low, medium-high, and high range of motion quartiles).

	Motion	Range of Motion (degrees)	Range of Motion category
Shoulder (glenohumeral)	Flexion	0 – 170	High
	Extension	0 – 67	Middle-low
	Abduction	0 – 180	High
	Adduction	0 – 180	High
	Internal rotation	0 – 48	Middle-low
	External rotation	0 – 105	Middle-high
Elbow (humeroulnar)	Flexion	0 – 150	High
	Extension	0 – 5	Low
	Abduction	**	Low
	Adduction	**	Low
Hip (acetabulo-femoral)	Flexion	0 – 130	Middle-high
	Extension	0 – 18	Low
	Abduction	0 – 48	Middle-low
	Adduction	0 – 31	Low
	Internal rotation	0 – 35	Low
	External rotation	0 – 48	Middle-low
Knee (tibiofemoral)	Flexion	0 – 140	High
	Extension	0 – 3	Low
	Medial translation	†	Low
	Lateral translation	†	Low
	Internal rotation	0 – 25	Low
	External rotation	0 – 45	Low

* Range of motion reference values sourced from Barnes, Van Steyn, & Fischer, 2001; Soucie et al., 2011; American Academy of Orthopaedic Surgeons, 1965; Zarins, Rowe, Harris, & Watkins, 1983

** Range of motion not recorded in the literature; presumed to be very minimal given the interlocking nature of the humerus and ulna

† Degree range not recorded in the literature, but observed as < 2mm under non-traumatic, non-pathological circumstances (Li et al., 2009).

Table I.2: Trace permutation results for comparing variance between antimeres. Traces were calculated as the summed variance for each joint or surface; traces were then compared to permuted traces derived from a random sample of pooled left and right sides. Significant p-values reflect differences in within-side trace values compared to pooled-side permutation traces.

Element	Left Side Trace	Right Side Trace	Difference Between Traces	<i>p</i> -value
<i>Joint</i>				
Shoulder	0.012	0.012	0.000	0.995
Elbow	0.014	0.013	0.001	0.618
Hip	0.019	0.017	0.002	0.388
Knee	0.007	0.007	0.000	0.229
<i>Articular Surface</i>				
Glenoid fossa	0.012	0.012	0.000	0.994
Humeral head	0.000	0.000	0.000	0.963
Distal humerus	0.000	0.000	0.000	0.852
Ulna	0.014	0.013	0.001	0.613
Acetabulum	0.019	0.017	0.002	0.379
Femoral head	0.000	0.000	0.000	0.829
Distal femur	0.000	0.000	0.000	0.883
Tibia	0.007	0.006	0.001	0.230

Table I.3: Trace permutation results for comparing variance between males and females. Traces were calculated as the summed variance for each joint or surface; traces were then compared to permuted traces derived from a random sample of pooled males and females. Significant p-values reflect differences in within-sex trace values compared to pooled-sex permutation traces.

	Female Trace		Male Trace		Difference Between Traces		<i>p</i> -value	
	Left side	Right side	Left side	Right side	Left side	Right side	Left side	Right side
<i>Joint</i>								
Shoulder	0.019	0.023	0.239	0.021	-0.004	0.002	0.012	0.226
Elbow	0.026	0.024	0.022	0.022	0.003	0.002	0.036	0.047
Hip	0.025	0.025	0.029	0.024	-0.004	0.001	0.363	0.679
Knee	0.016	0.015	0.015	0.013	0.001	0.002	0.406	0.034
<i>Articular Surface</i>								
Glenoid fossa	0.013	0.013	0.011	0.011	0.002	0.002	0.026	0.166
Humeral head	0.000	0.000	0.000	0.000	0.000	0.000	0.345*	0.696
Distal humerus	0.000	0.000	0.000	0.000	0.000	0.000	0.887*	0.876
Ulna	0.015	0.012	0.013	0.013	0.002	-0.001	0.166	0.077
Femoral head	0.000	0.000	0.000	0.000	0.000	0.000	0.021*	0.204
Distal femur	0.000	0.000	0.000	0.000	0.000	0.000	0.342*	0.920
Tibia	0.007	0.007	0.007	0.007	0.000	0.001	0.277	0.646

* Trace differences are < 0.000

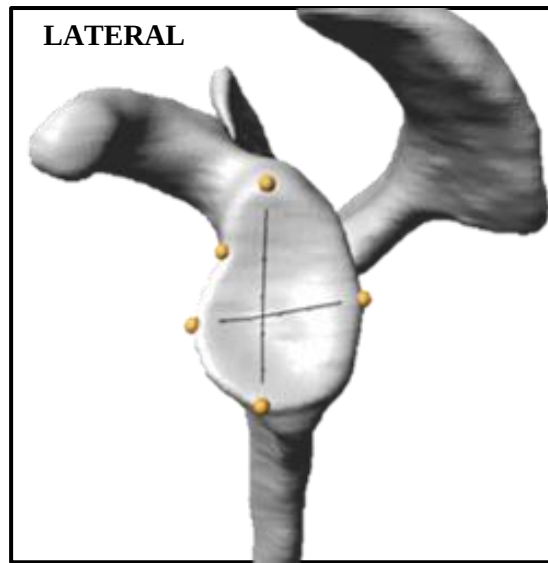


Figure I.1: Scapula landmarks (n = 5) and curves (n = 2)

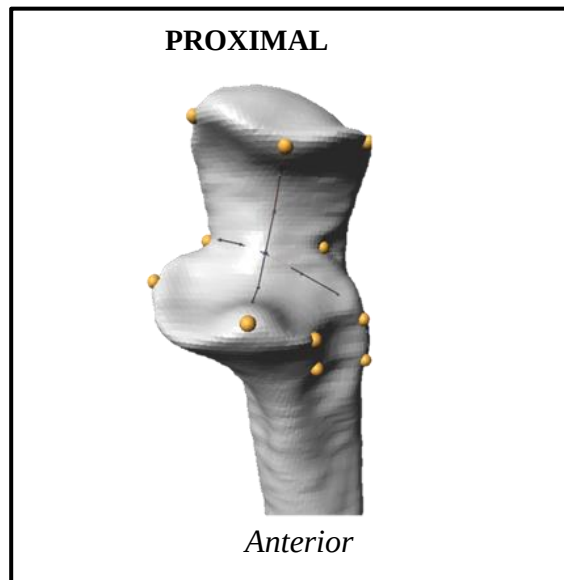


Figure I.2: Ulna landmarks (n = 11; adapted from Tallman 2013) and curves (n = 2)

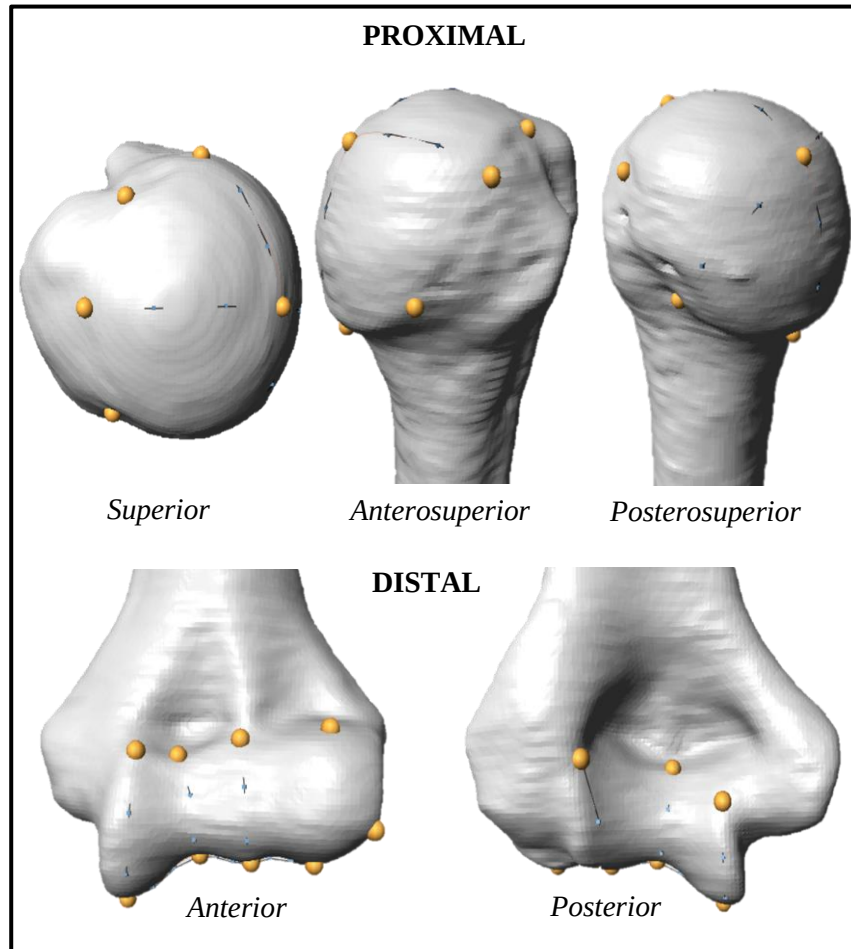


Figure I.3: Proximal humerus landmarks (n = 8; adapted from Arias-Martorell et al. 2015) and curves (n = 2). Distal humerus landmarks (n = 12; adapted from Tallman 2013) and curves (n = 4)

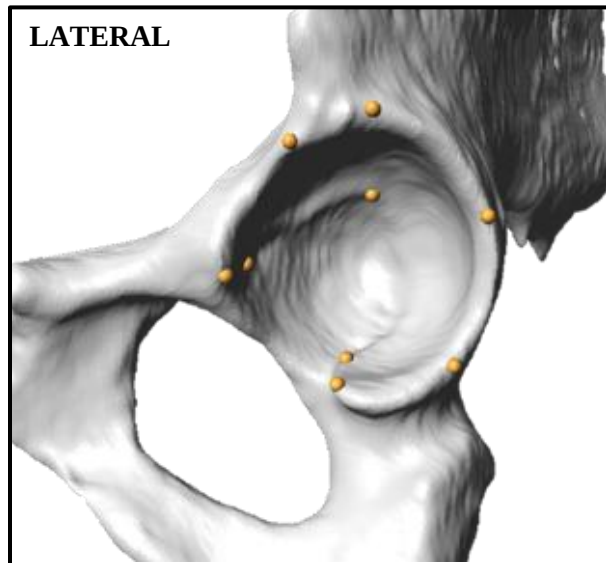


Figure I.4: Os coxa landmarks (n = 9; adapted from Millan et al. 2015)

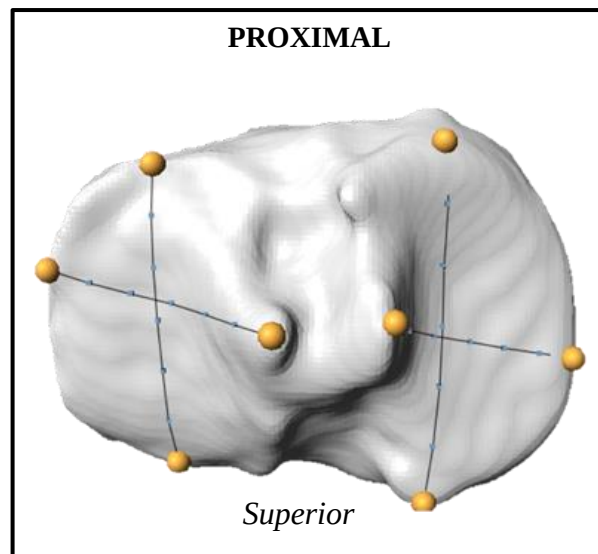


Figure I.5: Tibia landmarks (n = 8; adapted from Tallman 2013) and curves (n = 4)

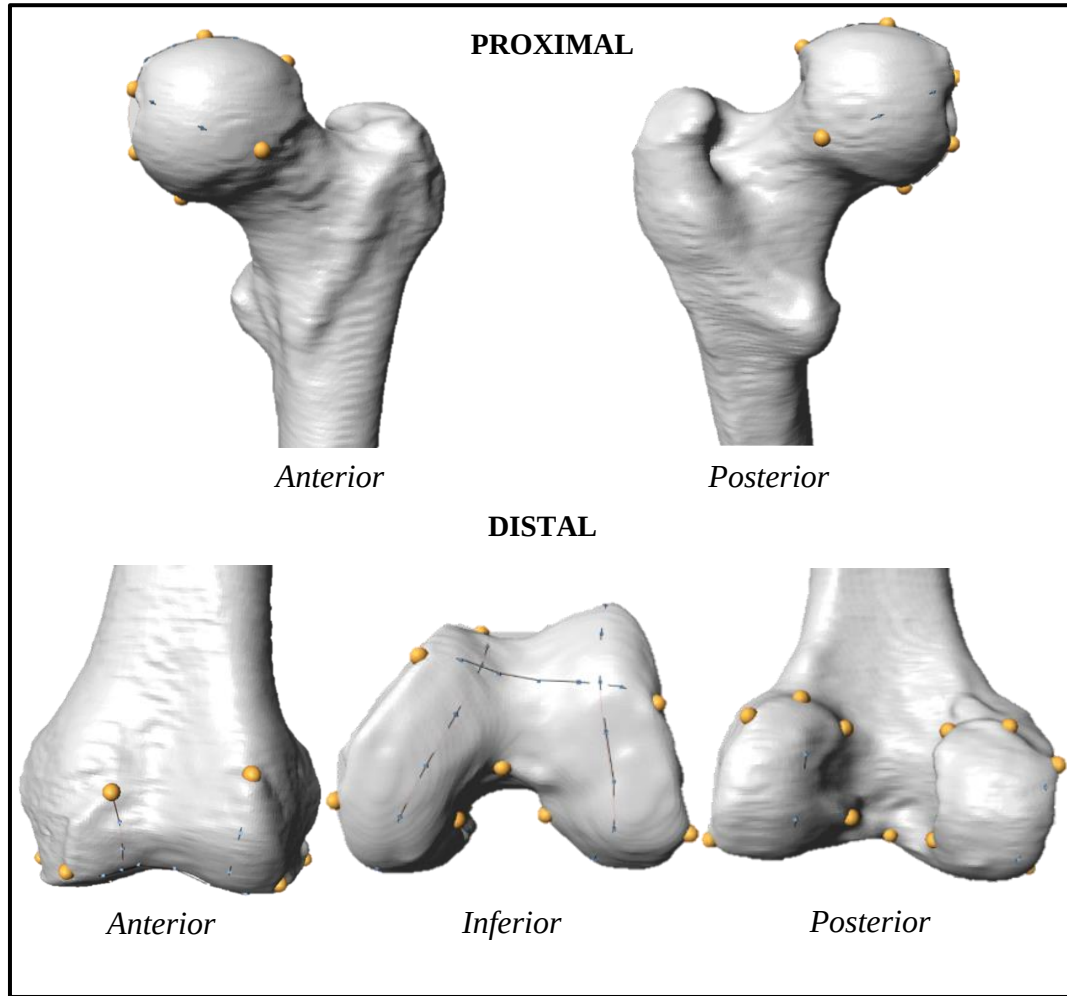


Figure I.6: Proximal femur landmarks (n = 7; adapted from Tallman 2010, Tallman 2013) and curves (n = 2). Distal femur landmarks (n = 15; adapted from Tallman 2013) and curves (n = 3)

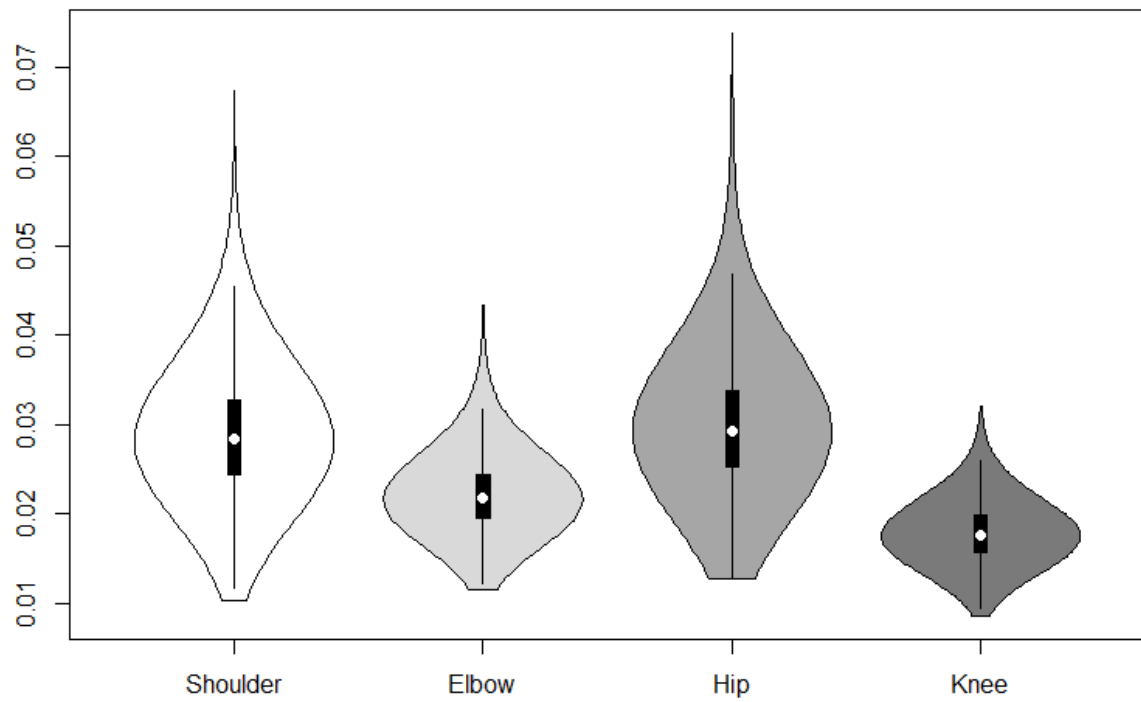


Figure I.7: Violin plot demonstrating root mean square distance distributions for each joint

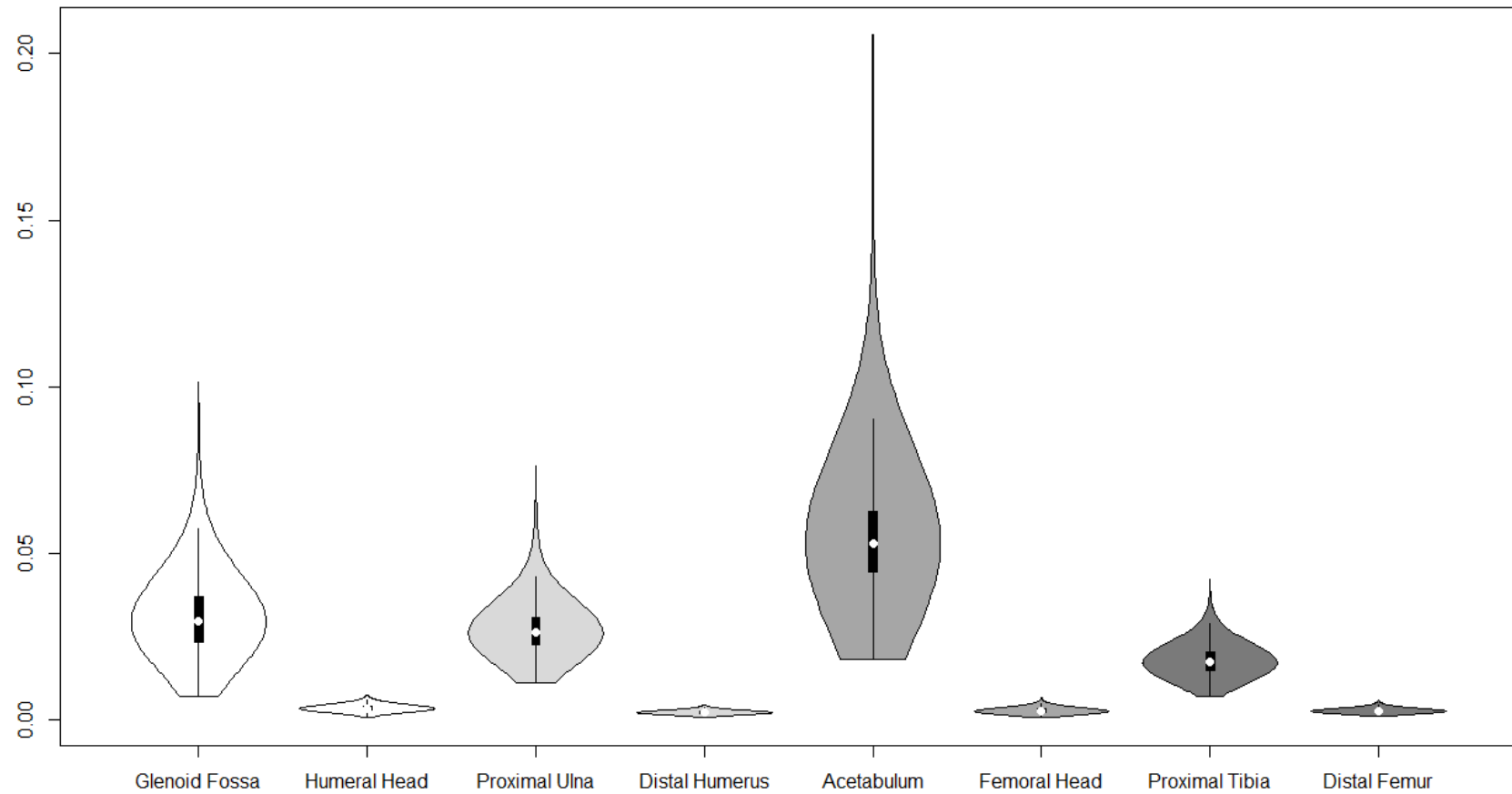


Figure I.8: Violin plot demonstrating root mean square distance distributions for individual articular surfaces

Table I.4: Scapula landmarks. All landmarks and curves contribute to the shoulder. Landmarks and contours developed by HH based on surface extrema outlined in Langley, Jantz, Ousley, Jantz, and Milner (2016)

LM#	Location	Definition
1	Glenoid fossa	Most superiorly projecting point on the glenoid margin
2	Glenoid fossa	Deepest point of incurvature on the superoanterior margin
3	Glenoid fossa	Most anteriorly projecting point on glenoid margin
4	Glenoid fossa	Most inferiorly projecting point on glenoid margin
5	Glenoid fossa	Most posteriorly projecting point on glenoid margin
C1	Glenoid fossa	Between LM1 & LM4, approximates superoinferior contour of glenoid fossa; Note: curve placed superior to inferior
C2	Glenoid fossa	Between LM3 & LM5, approximates AP contour of glenoid fossa; Note: curve placed ventral to dorsal

Table I.5: Humerus landmarks. Landmarks 1-8 and C1-C2 contribute to the shoulder; landmarks 9-20 and C3-C6 contribute to the elbow. Proximal humerus landmarks were adapted from Arias-Martorell, Tallman, Potau, Bello-Hellegouarch, and Perez-Perez (2015). Distal humerus landmarks were adapted from Tallman (2013). Contours defined by HH.

LM#	Location	Definition
1	Humeral head	Viewed superiorly: Closest point to the bicipital groove on the articular perimeter
2	Humeral head	Viewed superiorly: the point of intersection between the lesser tubercle and the articular perimeter
3	Humeral head	Viewed superiorly: point of intersection between the greater tubercle and the articular surface
4	Humeral head	Viewed medially: point of maximum curvature on the articular perimeter
5	Humeral head	Maximum point of curvature of the articular surface in the A-P plane
6	Humeral head	Midpoint between 1 and 3
7	Humeral head	Midpoint between 3 and 4 (posterior)
8	Humeral head	Midpoint between 2 and 4 (anterior)
C1	Humeral head	Connecting 6, 5, and 4; P-D contour (from proximal to distal)
C2	Humeral head	Connecting 2, 5, and 7: A-P contour (taken A->P)
9	Trochlea	Viewed anteriorly: proximomedial extreme of the trochlea
10	Trochlea	Viewed anteriorly: deepest incurvature on the proximal aspect of the trochlear groove
11	Trochlea	Viewed anteriorly: proximolateral extreme of the trochlea
12	Capitulum	Most proximal point of the capitulum
13	Capitulum	Most lateral-anterior point of the capitulum
14	Capitulum	Most distal point of the capitulum; confirm in lateral view
15	Trochlea	Distolateral extreme of the trochlea; in line with 6 and 7
16	Trochlea	Deepest incurvature on the distal aspect of the trochlear groove; in line with 6 and 7
17	Trochlea	Distomedial extreme of the trochlea; confirm in medial view
18	Trochlea	Viewed posteriorly: proximomedial extreme of the trochlea
19	Trochlea	Viewed posteriorly: proximal margin of the trochlea in line with the trochlear groove (distal to where bone slopes toward the olecranon fossa)
20	Trochlea	Viewed posteriorly: proximolateral extreme of the trochlea (distal to where bone slopes toward olecranon fossa)
C3	Trochlea	Connecting 9, 17, and 18
C4	Trochlea	Connecting 10, 16, 19
C5	Trochlea	Connecting 11, 15, 20
C6	Trochlea	Connecting 14-17

Table I.6: Ulna landmarks. All landmarks and curves contribute to the elbow. Landmarks were adapted from Tallman (2013). Contours defined by HH.

LM#	Location	Definition
1	Trochlear facet	Proximomedial extreme of trochlear facet margin
2	Trochlear facet	Most proximal and anteriorly-projecting point of the trochlear facet, on the guiding ridge
3	Trochlear facet	Proximolateral extreme of trochlear facet margin
4	Trochlear facet	Point of maximum constriction on the lateral trochlear margin
5	Trochlear facet	Distolateral extreme of trochlear facet margin
6	Trochlear facet	Most distal and anteriorly-projecting point of the trochlear facet, on the guiding ridge
7	Radial facet	Most proximal and anterior point of the radial facet
8	Radial facet	Most distal and anterior point of the radial facet
9	Radial facet	Most distal and posterior point of the radial facet
10	Radial facet	Most proximal and posterior point of the radial facet
11	Trochlear facet	Point of maximum constriction on the medial trochlear margin
C1	Trochlear facet	Between 2 and 6, and midpoint; to approximate curvature of semilunar notch
C2	Trochlear facet, radial notch	Connecting 4, C1 midpoint, 10, and 9; to approximate M-L curvature of the surface

Table I.7: Os coxa landmarks. All landmarks contribute to the hip. Landmarks were adapted from San Millán et al. (2015).

LM#	Location	Definition
1	Major lunate margin	The ventral terminal point for the major lunate margin
2	Major lunate margin	Point on major lunate margin where it joins with ventral ilium
3	Major lunate margin	Point where lunate margin aligns with dorsal ilium
4	Major lunate margin	Midpoint between 3 and 5
5	Major lunate margin	Point where lunate margin joins with ischium
6	Major lunate margin	The caudal terminal point for the major lunate margin
7	Minor lunate margin	The caudal terminal point for the minor lunate margin
8	Minor lunate margin	The greatest incurvature of the minor lunate margin
9	Minor lunate margin	The ventral terminal point for the minor lunate margin

Table I.8: Femur landmarks. Landmarks 1-7 and curves 1 & 2 contribute to the hip; landmarks 8-22 and curves 3-5 contribute to the knee. Landmarks were adapted from Tallman (2013). Contours defined by HH.

LM#	Location	Definition
1	Femoral head	When viewed anteriorly AND posteriorly, the point where the articular margin meets superior margin of femoral neck
2	Femoral head	Taken as a midpoint between 1 and 3
3	Femoral head	Cranial margin of fovea capitis
4	Femoral head	Caudal margin of fovea capitis
5	Femoral head	When viewed anteriorly AND posteriorly, the point where the articular margin meets the inferior margin of the femoral neck
6	Femoral head	Anterior midpoint between 1 and 5
7	Femoral head	Posterior midpoint between 1 and 5
C1	Femoral head	Connecting 3, 4, 1, and 5; approximates an M-L contour (collected proximal to distal)
C2	Femoral head	Between 3, 6, and 7; approximates an A-P contour (collected ant to post)
8	Patellar surface	Most proximolateral point of the patellar articular border
9	Patellar surface	Most proximomedial point of the patellar articular border
10	Lateral condyle	When viewed distally, the medial-most constriction of the lateral epicondyle
11	Lateral condyle	When viewed distally, most lateral point on lateral condyle
12	Medial condyle	When viewed distally, the lateral-most constriction of the medial epicondyle
13	Medial condyle	When viewed distally, the medial-most projection of the medial epicondyle
14	Medial condyle	When viewed distally, greatest incurvature of intercondylar notch
15	Lateral condyle	When viewed posteriorly, the most distomedial point on lateral condyle
16	Lateral condyle	When viewed posteriorly, most proximomedial point on lateral condyle
17	Lateral condyle	When viewed posteriorly, most proximolateral point on lateral condyle
18	Lateral condyle	Midpoint between 16 and 17
19	Medial condyle	When viewed posteriorly, the distolateral point on the medial condyle
20	Medial condyle	When viewed posteriorly, the proximolateral point on the medial condyle
21	Medial condyle	When viewed posteriorly, the proximomedial point on the medial condyle
22	Medial condyle	Midpoint between 20 and 21
C3	Patellar surface	Between 10, 12 and a midpoint (collected lateral to medial)
C4	Lateral condyle	Between 8, 18, a midpoint between 11 and 15, and a midpoint between 10 and C3 midpoint
C5	Medial condyle	Between 9, 22, a midpoint between 13 and 19, and a midpoint between 12 and C3 midpoint

Table I.9: Tibia landmarks. All landmarks and curves contribute to the knee. Landmarks were adapted from Tallman (2013). Contours defined by HH.

LM#	Location	Definition
1	Lateral condyle	Medial-most point on the lateral tibial condyle
2	Lateral condyle	Posterior-most point on the lateral tibial condyle
3	Lateral condyle	Lateral-most point on the lateral tibial condyle
4	Lateral condyle	Anterior-most point on the lateral tibial condyle=
5	Medial condyle	Lateral-most point on the medial tibial condyle
6	Medial condyle	Posterior-most point on the medial tibial condyle
7	Medial condyle	Medial-most point on the medial tibial condyle
8	Medial condyle	Anterior-most point on the medial tibial condyle
C1	Lateral condyle	Between 4, 2, and a midpoint – anterior to posterior
C2	Lateral condyle	Between 1, 3, and a midpoint – medial to lateral
C3	Medial condyle	Between 6, 8, and a midpoint – anterior to posterior
C4	Medial condyle	Between 5, 7 and a midpoint - medial to lateral

CHAPTER III:
THE APPORTIONMENT OF COVARIANCE IN HUMAN LIMB BONE
SYNOVIAL JOINT ARTICULAR SURFACES

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Abstract

Objectives: Human limbs exemplify a tension between function and development—our upper and lower limbs are more functionally divergent than any other primate, yet they are inherently linked by near-identical developmental pathways. Compounded with this paradox, limb synovial joints exhibit complex shapes that must achieve coordinated growth and reciprocal fit with adjacent morphology, making joints acutely representative of the trade-offs of the human skeleton. These often-antagonistic demands of function, mobility, and stability presumably dictate the coordination among joint articular shapes, but the structure of morphological covariance within and among joints is unknown. This study uses three-dimensional geometric morphometrics of the shoulder, elbow, hip, and knee to determine how articular covariance is structured in relation to complementary or analogous function in modern human limb joints.

Methods: Surface models were created from the CT scans of 200 modern skeletons from the Bass Donated Skeletal Collection. Landmarks were collected on the shoulder (glenohumeral), elbow (humeroulnar), hip (acetabulofemoral), and knee (tibiofemoral) joints. Two-block partial least squares were conducted to determine associations between surfaces of complementary function (e.g., the glenoid fossa and humeral head), analogous function (e.g., the humeral head and femoral head), and within-bone covariance (e.g., the proximal and distal humerus).

Results: All articulating surfaces that are complementary for function exhibit significant covariance, though the strength of these relationships appears to be unrelated to the amount of meniscal or labral padding present in the joint. Upper and lower limb articulations that are analogous for function exhibit even higher covariance than directly articulating morphologies but it is unclear whether these relationships are due to function alone. Within-element covariance exhibits the strongest association; these results collectively suggest greater overall covariance in the upper limb.

Discussion: Joint function alone, whether it be complementary or analogous, does not appear to promote strong covariance between functionally related articulations, and the observed hierarchy in covariance does not follow predictions based on the amount of cartilage present. The analogous surfaces of the proximal and distal humerus and femur share the additional relationship of being serially homologous, which may result in the strong covariance observed. The observation that within-element covariance is higher than between-element covariance is consistent with prior studies. These results may reflect deeper patterns of primate limb evolution and coordination and have the potential for modern clinical implications.

Introduction

Coordinated variation, or covariation, among morphological traits indicates possible underlying shared development or convergent function (Agosto & Auerbach, 2021; Rolian, 2009, 2014; Unger, Devine, Hallgrímsson, & Rolian, 2021; Young, 2017; Young, Wagner, & Hallgrímsson, 2010), and provides a framework for understanding the independence or interdependence of evolutionary trajectories among aspects of morphology (Savell, Auerbach, & Roseman, 2016). Highly independent traits will more easily allow morphological characteristics

to diverge from one another. Limbs are a prominent point of interest for covariance studies, especially in functionally divergent species like humans, as underlying shared developmental cascades (serial homology) coincide with and may even aid the functional divergence of the upper and lower limbs relative to nonhuman primates (Rolian, 2009; Young et al., 2010). To this end, limb covariation studies are uniquely positioned to explore how interspecific differences in functional divergence may manifest relative to differential limb covariance (Tallman, 2013, 2016; Young & Hallgrímsson, 2005).

Despite the frequent inclusion of articular and periarticular landmarks in limb covariance studies (Martín-Serra, Figueirido, Pérez-Claros, & Palmqvist, 2015; Tallman, 2013, 2016; Young & Hallgrímsson, 2005), the synovial joints of the limbs and their respective functions are not often the focus of research inquiry. Yet as posture, limb range of motion, and locomotion change over the course of evolution, joints are also changing in concert with one another, potentially resulting in a joint-specific structure of covariance that reflects their unique functions and underlying development (Kelly & Sears, 2011; Sears, Bianchi, Powers, & Beck, 2013; Sears, Capellini, & Diogo, 2015). Presumably, the most proximate influence on joint morphology is the shape of neighboring morphology with which it must directly articulate (Carter & Wong, 1988; Chijimatsu & Saito, 2019; Zhou, 2021); in other words, complex joint shapes must achieve a coordinated growth whereby complementary components can function together. The strength of this relationship may be tempered by the additional presence of menisci or labra which can vary in thickness and serve to partially accommodate for articular conformity, among other functions (Graichen et al., 2003; Shepherd & Seedhom, 1999; Springer et al., 1998). Another potential source of covariance is the related roles of functionally analogous articular surfaces—those

articulations in the upper and lower limbs that perform relatively the same movements for their respective joints (e.g., the humeral head and femoral head).

In this study, patterns of covariance are examined among joint surfaces to investigate three broad questions derived from the above assumptions. First, I hypothesize that complementary function will promote covariance between directly articulating surfaces (e.g., the femoral head and acetabulum). However, given that cartilage exists in varying degrees in each of these joints and presumably accommodates a portion of each joint's articular fit, I also expect that more cartilage will reduce the covariance between directly articulating surface shapes. Therefore, the humeroulnar elbow, the acetabulofemoral hip, the glenohumeral shoulder, and the tibiofemoral knee will exhibit decreasing amounts of covariance, respectively. One caveat, based on the analysis of variation in the articular surfaces (Horbaly et al., Chapter II), is that the greatest variance in concave surfaces occurs in the hip and shoulder, and as such may result in less coordinated variation than the elbow or knee; this provides an alternative hypothesis for the hierarchy in patterns of covariation. Second, I hypothesize that analogous function will promote covariance, but to a lesser degree than directly articulating morphologies. Finally, I hypothesize that within-element covariance will be greater than covariation among articulating and functionally analogous surfaces. Given the findings of Horbaly et al. (Chapter II), which demonstrate low variance of the proximal and distal articulations of the humerus and femur relative to their articulating surfaces, within-bone comparisons between these articulations are expected to show a strong association. If true, this finding would be consistent with other previous work demonstrating stronger within- than between-element covariance (Young & Hallgrímsson, 2005).

Context for Covariation in the Limbs: Indications from Studies of Limb Variance

Before assessing my hypotheses, it is useful to contextualize this study's expectations with knowledge gleaned through studies of limb variation in humans. As noted above, in a recent study by the author and colleagues, an analysis of the distribution of variance among articular surfaces revealed two novel findings that are relevant to our study of joint articular surface shape covariance. First, Horbaly et al. (Chapter II) found that concave joint surfaces (e.g., the acetabulum or the semilunar notch of the ulna) have significantly more variation than their articulating convex surfaces (e.g., the femoral head or the distal humerus). They concluded that this pattern could relate to differences in underlying genetic variation between these surfaces (Pacifici, Koyama, & Iwamoto, 2005; Sears, 2014), or could also relate to differences in the force transmission across joint surfaces that could affect development under chondral modeling theory (Frost, 1979; Hamrick, 1999). Second, Horbaly et al. found that variance was greatest in the concave surfaces of the acetabulum and glenoid fossa, which may relate to the degree of movement possible at these joints versus others. I expect that these patterns of variation will be mirrored in the patterns of covariance among joints, where the greater discrepancy in variances between the convex and concave articulating surfaces at the more proximal joint in each limb, in addition to the greater range of motion and presence of labra at the shoulder and hip, could result in overall lower covariance in these joints.

In studies that establish patterns of variation among limbs and limb segments, a handful of additional broad patterns are consistently demonstrated. Distal limb segments exhibit a greater accumulation of variation than proximal limb segments (Holliday & Ruff, 2001; c.f. Shaw, Stock, Davies, & Ryan, 2014; Stock, 2006), perhaps due to the cascading nature of variance-generating processes of limb outgrowth during development (Hallgrímsson et al., 2009;

Hallgrímsson, Willmore, & Hall, 2002; Škrabar, Turner, Pallares, Harr, & Tautz, 2018).

Furthermore, limb asymmetry among humans is greater in the upper limb where side-biased handedness underlays most lateralized limb activities (Auerbach & Ruff, 2006; Ingelmark, 1974; Plochocki, 2004; Ruff & Jones, 1981; Sakaue, 1998; Schultz, 1937; Trinkaus, Churchill, & Ruff, 1994). How, or if, these patterns of variation in limbs are reflected by patterns of covariation in the four joints examined here—e.g., lower covariances in the upper limb or on distal joints—will be taken into account in interpretations of the results.

Materials and Methods

Here I use the same sample as Horbaly et al. (Chapter II). Computed tomography (CT) scans were sampled from 200 adult individuals (84 females and 116 males) aged between 24 and 93. The individuals in the sample were selected for their lack of documented or observable bone pathologies, apparent degeneration, or medical intervention (namely arthroplasty) on the joints under study. CT scans consist of isotropic voxels at a resolution of 0.625mm^3 , and were obtained as part of earlier collaborative research (Shirley, Wilson, & Jantz, 2011; Sylvester, Merkl, & Mahfouz, 2008). These scans were obtained after skeletal elements were defleshed, but despite the lack of articular cartilages on CT scans of the bones, dry bone morphology alone is known to reflect variation in shape (Horbaly et al., Chapter II; Martelli & Pinskerova, 2002; Sylvester, 2015) and is thus appropriate for answering the questions posed by the current study.

As this study seeks to explore the hierarchy of morphological covariance in the major joints of the upper and lower limb, the glenohumeral, humeroulnar, acetabulofemoral, and tibiofemoral joints were observed, as in Horbaly et al. (Chapter II). The varying ranges of motion exhibited by the selected joints require different degrees of articular conformity which

presumably will relate to shape covariance between two articulating components. To assess the second hypothesis, it is further necessary to examine functionally analogous joints that routinely experience different biomechanical demands due to limb divergence and locomotor specialization. Individual articular components of these joints also serve as upper and lower limb analogues for function (e.g., humeral head/femoral head).

Geometric morphometric data capture methods in this study match those of Horbaly et al. (Chapter II). Skeletal elements were segmented from CT image stacks using Avizo 2021.1 or an automated custom routine in Matlab 2021b. Landmarks were placed on the resulting surface models of these bones using Stratovan Checkpoint. Landmarks followed published definitions (Arias-Martorell, Tallman, Potau, Bello-Hellegouarch, & Perez-Perez, 2015; San Millán, Kaliontzopoulou, Rissech, & Turbón, 2015; Tallman, 2013, 2016); novel landmarks and semilandmark contours were defined by HH. Full landmark definitions are available in Horbaly et al. (Chapter II). After a period of calibrating for landmark placement on a separate sample, HH landmarked four full sets of joint surfaces (a total of 600 landmarks) and confirmed that the landmarks were placed consistently using a paired t-test ($p > 0.05$).

To test for covariance between shapes, a two-block partial least squares (2B-PLS) analysis was implemented on Procrustes shape coordinates using the ‘geomorph’ package (Adams, Collyer, Kaliontzopoulou, & Baken, 2021; Baken, Collyer, Kaliontzopoulou, & Adams, 2021) in R (R Core Team, 2021). 2B-PLS determines whether two landmark sets (Procrustes shape variables in blocks) are significantly associated with one another, following the precedent set by Rohlf and Corti (2000). In this approach, the partitioning of a correlation matrix among traits—or covariance in the case of morphometric landmarks (as argued in Rohlf and Corti (2000)—into R matrices that contain the covariance between the unstandardized shape variables

and the classifying variable under study; in the present case, these are different set designations for articular surfaces. By calculating the correlations between the first singular blocks of each shape under analysis (e.g., humeral head and femoral head), we obtain the *r*-PLS coefficient which can be interpreted similarly to a Pearson correlation coefficient with a range between zero and positive one for two blocks of three-dimensional landmark data. The two landmark sets compared in each 2B-PLS test were either the convex and concave components of a joint (e.g., glenoid fossa/humeral head), the surface pairs that are analogous for function (e.g., humeral head/femoral head), or the articulations representing within-element comparisons (e.g., humeral head/distal humerus). Horbaly et al. (Chapter II) established that there are not significant differences in variance between antimeres and so only left side joints and articular surfaces are analyzed here. Likewise, a preliminary 2B-PLS analysis for each joint and articular surface is conducted here to determine whether males and females exhibit similar covariance structures and thus can be pooled for the remaining analyses.

Results

A two-block PLS analysis comparing covariance matrices of all joints between the sexes indicates that there is no statistical difference in the pattern of overall joint covariance structure between females and males ($p < 0.001$; Table II.1). The similarities are more marked for the glenohumeral and knee joints, but the lack of statistical differences in the covariance matrices supports the combination of females and males in subsequent analyses.

Overall, articulating joint surfaces covary, though with unequal magnitudes. All joints exhibit significant associations between their articulating convex and concave surfaces ($p < 0.02$ for all joints; Table II.2a). The correlations between these blocks of shape variables have *r*-PLS

values ranging from 0.34 to 0.53. Notably, the highest covariance in shape occurs in the elbow, followed by the knee, and then similar correlations exist within the proximal joints of the upper and lower limbs.

Surfaces that are analogous for function present mixed significant covariance. The analogous surfaces of the humerus and femur (proximal to proximal and distal to distal) have significant shape associations (r -PLS = 0.60, proximal, 0.62, distal surfaces; $p < 0.01$) (Table II.2b). Two of the analogous surface pairs (acetabulum/glenoid fossa, ulnar trochlear notch/tibial condyles) do not show a significant covariance (r -PLS = 0.25 and 0.35, respectively).

The inclusion of both the proximal and distal articulations of the humerus and femur allows for within-element covariance to be assessed for these bones (Table II.2c). While within-element covariance cannot be established for all bones under study, the proximal and distal ends of the humerus and femur do constitute one component for each joint of the shoulder, elbow, hip, and knee. Results indicate significant covariance ($p < 0.01$), with the humerus showing stronger covariance between its proximal and distal ends (r -PLS = 0.90) than is observed in the femur (r -PLS = 0.75).

Discussion

The results broadly support the hypotheses outlined in the Introduction, with notable exceptions. All directly articulating surface pairs exhibit significant covariance in articular shapes. It was expected that the relative hierarchy of covariance among these joints would be structured according to the amount of accessory cartilage (labra or menisci) present in each joint, with more accessory cartilage accommodating articular fit and thus reducing the need for strong shape association. This hypothesis was not supported, but instead the results in Table II.2a

support the alternative hypothesis that the greater variances in concave surfaces at the hip and shoulder would drive lower covariance at these joints compared with the knee and elbow. Further, covariances of the more distal joints are greater than proximal joints. The second hypothesis is partially supported (Table II.2b): analogous articular surfaces of the upper and lower limb covary, but only the morphologies of the humerus and femur are significantly covariant and, contrary to expectations, exhibit stronger morphological relationships than any of the directly articulating morphologies. In contrast, the hypothesis that covariance would be greatest within elements is borne out by the results (Table II.2c). These results are unpacked further below.

Covariance among articulating joint surfaces

The lack of elaborate cartilaginous padding such as a labrum or meniscus does correspond with greater covariance, as is evidenced by the elbow exhibiting the strongest association between its distal humerus and semilunar notch articulations. However, when labra or menisci are present as is the case for the remaining joints under study, their varying thicknesses do not seem to dictate the hierarchy of covariance. If shape covariance were tied to accessory cartilage thickness, the elbow would be followed by the hip, the shoulder, and finally the knee which is understood to have the most extensive cartilage of the four joints studied here due to the presence of menisci (Shepherd & Seedhom, 1999). Yet contrary to expectations, the knee exhibited the second strongest covariance, followed by the shoulder and the hip, which exhibited comparably low covariance.

This unexpected greater covariance in the knee than the hip or shoulder suggests that covariance between articulating surfaces is not dependent on the amount of accessory cartilage accommodating articular fit for a particular joint. Rather, in comparison with the hip and

shoulder, the elbow and knee are more distal, have more limited ranges of motion, and as prior work has established (Horbaly et al., Chapter II), exhibit lower morphological variance across a modern population. This relationship between the strength of articular covariance and the amount of variation observed for each joint by Horbaly et al. (Chapter II) contributes to a body of contrasting evidence concerning the amount of variation present in distal elements within the limbs. While some studies (e.g., Auerbach & Ruff, 2006; Holliday & Ruff, 2001) suggest that length, articular dimensions, and diaphyseal properties have greater variation in distal limb elements than proximal elements (e.g., zeugopods versus stylopods), others (e.g., Shaw et al., 2014; Stock, 2006) present evidence that there is less variance distally, especially in diaphyseal dimensions. In the case of the latter papers, the lower variance in distal elements is argued to be a consequence of tissue economy (Stock, 2006) during growth and development. Lower variance and higher covariance in distal joints, along with the evidence from Shaw et al. (2014) and Stock (2006) collectively support the argument for decreased variation in distalized morphologies within limbs.

The relative strength of association in articular shapes may be best explained by joint function, which may be classified coarsely into differences in ranges of motion (ROM). ROM classifications are detailed in Horbaly et al. (Chapter II) and follow commonly accepted reference values (Barnes, Van Steyn, & Fischer, 2001; Li et al., 2009; Soucie et al., 2011; American Academy of Orthopaedic Surgeons, 1965; Zarins, Rowe, Harris, & Watkins, 1983). A higher ROM joint like the shoulder or hip may allow for greater morphological independence between its articular components because the logistics of shape for these ball and socket joints are simple—smooth, rounded expanses of articular surface that accommodate multidirectional movement. Alternatively, lower ROM joints such as the elbow and knee require stability and

through their morphology impede movement to fewer planes, resulting in a more interlocking morphological structure. The ulnar semilunar notch exhibits a guiding ridge that must correspond to the trochlear constriction of the humerus to successfully prevent mediolateral displacement, and overflexion and overextension are inhibited by the ulna's coracoid and olecranon processes locking into their respective fossae on the distal humerus. Though these fossae were not included in the distal humeral landmark set, the humeral trochlea, which was quantified here, must be shaped in such a way that it successfully guides the ulna into these fossae during peak flexion/extension. Similarly, the major movement of the knee is flexion and extension, and while some slight abduction, adduction, and rotation occur at the knee, this joint must largely be stable in a mediolateral direction and at the extremes of flexion or extension due to this joint's crucial role in locomotion. Consequently, the location of the intercondylar notch on the distal femur must coordinate closely with the location of the medial and lateral intercondylar tubercles, bony components of the tibia that act as anchors for two of the major stabilizing ligaments of the knee, the anterior and posterior cruciate ligaments. It is possible that because a portion of the knee's "interlocking" nature is constructed by these soft tissue ligaments running between the femoral condyles rather than a bony structure, this may explain the lower covariance of the tibiofemoral joint compared to the humeroulnar joint, where the interlocking morphology is solely constructed by the bony tissue.

This also further develops the prior finding by Horbaly et al. (Chapter II) that concave surfaces, especially the glenoid fossa and acetabulum, have significantly greater variance than their articulating convex surfaces. The discrepancy in amounts of variance between, for example, the humeral head and glenoid fossa also provides opportunity for lower covariance between these articular surfaces. Thus, greater mobility and greater morphological mismatch in variance

occur at the ball-and-socket joints, and so produce lower covariation irrespective of the amounts of articular cartilage present.

The increased potential for mismatch in the ball-and-socket joints may point to functional and injury implications for these joints, as it could be that the underlying shape of the bony anatomy leads to joint degeneration such as osteoarthritis. The knee and hip are two of the most common joints to develop osteoarthritis; given their biomechanical relationship as load-bearing joints, as well as their structural association via the involvement of the femur, it may be that acetabulofemoral mismatch accelerates the onset of osteoarthritis at one or both of these locations. Studies have identified relationships between hip and knee osteoarthritis due to disease- or arthroplasty-induced gait alteration (Manfrini, Campanacci, Spinnato, & Benedetti, 2020; Shakoor, Block, Shott, & Case, 2002; Shakoor, Hurwitz, Block, Shott, & Case, 2003), though whether disease onset and progression is partially due to higher incidences of shape mismatches at the hip as predicted by the collective results of the present study and Horbaly et al. (Chapter II) is unknown.

Covariance between analogous articular surfaces

While not all functionally analogous pairs exhibited significant relationships as predicted, it is perhaps no surprise that the humeral and femoral pairs did. In addition to their proximal and distal components being functionally analogous to one another, the humerus and femur are also serially homologous—they both comprise the stylopod (proximal segment) of their respective limbs and thus are formed via the deployment of similar developmental cascades (Towers & Tickle, 2009a, 2009b; Young & Hallgrímsson, 2005). The corresponding articulations of the humerus and femur, then, are *both* broadly homologous for development and analogous for function, whereas directly articulating components of a joint—while part of the same limb—

belong to distinct limb segments (e.g., stylopod vs zeugopod) and are complementary, rather than analogous, for function. This suggests that the covariance expected due to spatial proximity and shared biomechanical environments is weaker than the covariance induced by developmental and functional factors; in other words, the combination of developmental homology and functional analogy of the humerus and femur seem to transcend their spatial disparity and differing biomechanical environments to produce a strong covariance relationship. These findings are consistent with other studies that have found the humerus and femur to be more covariant than other limb bones (Martín-Serra et al., 2015; Tallman, 2013; Young & Hallgrímsson, 2005). It also reflects the size of these joints closely paralleling each other in estimates of body size in Old World primates, though the scaling of the humeral head and femoral head may not be the same across taxa (Ruff, 2002, 2003).

Why were significant covariance relationships not observed for the other surface pairs? The ulna and tibia are functionally analogous with one another as the major concave component of the upper and lower limb hinge joints, respectively. However, they are not developmentally homologous like the humerus and femur. Various knockout studies have repeatedly demonstrated the homologous relationship between zeugopod elements of the radius and tibia, and respectively, the ulna and fibula (Fraser & Robarts, 1914; Lewin, Opitz, & Reynolds, 1986; Martínez-Frías, Frías, & Opitz, 1998; Winter, 1988). Thus, the proximal ulna/proximal tibia comparison in the present study is unique in that it represents analogous function in the absence of shared development. This suggests that function alone may not be a strong enough driver of joint shape covariance, and that significant relationships between other upper and lower limb articular pairs like the humeral head/femoral head and distal humerus/distal femur—which are

both serially homologous as well as analogous for function—may be predominantly structured this way as a result of development.

As the concave girdle joint elements, the glenoid fossa of the scapula and acetabulum of the os coxa are analogous for function, yet like the proximal ulna and tibia, they do not exhibit a significant covariance relationship in their shapes. This is consistent with existing data on tetrapod pectoral and pelvic girdles and suggests these bones are less integrated than the elements comprising the major long bones within limbs (Pellegrini, Pantano, Fumi, Lucchini, & Forabosco, 2001; Sears et al., 2015). Unlike the upper and lower limb elements that derive from common progenitor cells, the evidence indicates the scapula and os coxa have different embryological origins from the limbs (Kardong, 1997; Young, 2004), from each other (Durland, Sferlazzo, Logan, & Burke, 2008; Huang, Christ, & Patel, 2006; Huang, Zhi, Patel, Wilting, & Christ, 2000; Malashichev, Borkhvardt, Christ, & Scaal, 2005; Malashichev, Christ, & Prots, 2008; Pomikal & Streicher, 2010) and subsequently exhibit distinct genetic regulation (Itou et al., 2012; Krawchuk et al., 2010; Sears et al., 2015; ten Berge, Brouwer, Korving, Martin, & Meijlink, 1998). Despite the glenoid fossa and acetabulum playing analogous functional roles in their “ball-and-socket” joints, the scapula and os coxae broadly perform different functions for their respective limbs. Therian mammal limb evolution saw a relaxation in the rigid connection between the scapula and trunk due to the reduction in the scapular coracoid; this relaxed connection resulted in a more mobilized shoulder girdle that serves as the most proximal point of rotation for the upper limb (Gasc, 2001; Schmidt & Fischer, 2009). Conversely, the os coxa maintains its rigid connection to the axial skeleton via its relatively immobile articulation with the sacrum, resulting in a functional difference between the two girdles (Martín-Serra et al., 2015). An exploration into both the evolution and development of these articular distinctions

among primates has potential to disentangle these deep evolutionary causes from more recent causes related to diversification of function, especially given the high morphological variation of the primate scapula (Agosto & Auerbach, in press; Preuschoft et al., 2010).

Covariance within elements

The inclusion of both the proximal and distal articulations of the humerus and femur allows for within-element covariance to be assessed for these bones. Both bones show significant and strong associations between their proximal and distal articulations. Higher within- element covariance than between-element covariance is consistent with prior studies (Young & Hallgrímsson, 2005). Furthermore, the humerus exhibits notably higher covariance between its proximal and distal ends compared to the articular covariance in the femur.

Taken together with the within-limb covariance values observed between directly articulating surfaces, these results paint a picture of greater covariance within the upper limb than the lower limb. Greater forelimb than hindlimb integration was observed by Young and Hallgrímsson (2005) in their interspecific study on hierarchical covariance among epiphyseal landmarks in vertebrate limb elements. They found that the bat and the gibbon—two species with extreme functional divergence between their upper and lower limbs—exhibited greater covariance among their forelimb bones of the humerus, radius, and metacarpals, whereas quadrupedal species demonstrated greater hindlimb covariance (among femur, tibia, metatarsals). While bats, gibbons, and humans share the common condition of functional divergence in their limbs due to locomotory specialization, humans are hindlimb dominant whereas bats and gibbons are forelimb dominant. The same pattern of strong forelimb covariance in these species

despite the different locomotory styles among them may suggest that decoupling of limb function may preferentially promote forelimb covariance, yet it is also likely that humans reflect a broader pan-primate pattern of limb bone covariation that has not been lost despite locomotor specializations for bipedality. Integration and evolvability studies should be conducted to explore this hypothesis more thoroughly.

Conclusion

This study further demonstrates that a hierarchy of variance and covariance is present among the articular surfaces of human limbs. The covariance hierarchy is not patterned based on the degree of meniscal or labral padding as was predicted, but rather appears to relate to the joint architecture that dictates range of motion. Where joints must allow large ranges of motion (e.g., in the shoulder and hip), the articulating surfaces are less complex and less covariant; joints that must limit motion in certain directions, such as the elbow and knee, exhibit more complex and interlocking topography, and so these features show greater correspondence. These results may have clinical implications, as reduced covariance and thus reduced morphological association could have repercussions for degeneration of articular surfaces. Further, the results of this paper reflect more general primate patterns, where the upper limb exhibits higher covariance than the lower limb, as well as a strong covariance between serially homologous and functionally analogous articulations of the humerus and femur. Overall, the patterns uncovered here evince the covariation of human articular surfaces as being shaped through shared developmental mechanisms as well as the effects of deeper evolutionary and functional relationships.

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APPENDIX II

Table II.1: 2B-PLS results between male and female covariance matrices for each joint. The critical alpha for all tests is 0.05; significant results are indicated with bold text.

Joint articular surfaces	<i>r</i>-PLS	Effect	<i>p</i>-value
Glenohumeral joint	0.842	5.636	0.001
Humeroulnar joint	0.632	5.604	0.001
Hip joint	0.678	3.547	0.001
Knee joint	0.875	7.659	0.001

Table II.1: Pooled 2B-PLS results for articulating joint surfaces (a), functionally analogous pairs (b), and within-element articular pairs (c) (n = 200, left-side articular surfaces). The critical alpha for all tests is 0.05; significant results are indicated with bold text.

Trait Pair	<i>r</i>-PLS	Effect	<i>p</i>-value
<i>a. Articulating surfaces</i>			
glenoid fossa – humeral head (shoulder)	0.35	2.831	0.004
distal humerus – ulnar trochlear notch (elbow)	0.53	4.765	0.001
acetabulum – femoral head (hip)	0.34	2.032	0.019
distal femur – tibial condyles (knee)	0.43	3.270	0.001
<i>b. Functionally analogous surfaces</i>			
glenoid fossa – acetabulum	0.25	0.011	0.497
humeral head – femoral head	0.60	6.563	0.001
distal humerus – distal femur	0.62	5.814	0.001
ulnar trochlear notch – tibial condyles	0.35	0.941	0.186
<i>c. Within-element surfaces</i>			
humeral head – distal humerus	0.90	7.48	0.001
femoral head – distal femur	0.75	7.77	0.001

CHAPTER IV: AN EXPLORATION OF DISTAL FEMUR SHAPE IN RELATION TO KNEE REPLACEMENT STATUS

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Horbaly as:

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Abstract

Objectives: Human joints are known to exhibit population-level variation in shape and are simultaneously common locations for skeletal degeneration and pathology, yet whether articular shape relates to an individual's propensity for joint degeneration is still under investigation. Prior studies seem to suggest joint shape does exhibit a relationship with joint pathology such as osteoarthritis, but explicit features of joint morphology have not been implicated. This study analyzes the distal femoral articulations from a contemporary skeletal population to investigate the relationship between an individual's knee replacement status and joint shape.

Methods: Three-dimensional shape data was collected from distal femora of 12 skeletons who received total knee arthroplasty (TKA) during life, and 35 skeletons who did not receive knee replacements (non-TKA) and can act as a comparative sample. Principal components analysis was used to visualize whether the TKA skeletons could be distinguished from the non-TKA group based on distal femoral shape, and wireframes were created to assist in visualization of specific shape changes along PCs. Pearson and canonical correlations tested for relationships between shape, PC1 and PC2, and donor biological data of stature and weight.

Results: PCA analysis shows that TKA skeletons do exhibit distinctive distal femoral shape compared to their non-TKA counterparts. Wireframes illustrate the major changes along PC1,

showing the anteriorization of the medial condyle curvature, as well as the medial rotation of the medial condyle, in TKA individuals. Correlations indicate no significant correspondence between PC1 and PC2 with donor stature and weight.

Discussion: The shape differences observed between groups in the present study cannot be explained by demographic attributes (stature, weight, age, sex), yet show clear distinctions between TKA and non-TKA groups. These findings support prior studies which identify an association between joint shape and disease onset or progression and contributes novel findings that implicate changes to the medial condyle that may drive this association. A comparison to the clinical literature provides evidence of increased wear on the anterior portion of the medial femoral condyle in individuals who undergo surgery for knee replacement, though future studies consisting of larger sample sizes and longitudinal observation are required to validate a connection between disease onset and the shape differences identified herein.

Introduction

Joint articular shape is known to vary within and among contemporary humans (Horbaly et al., Chapter II; Horbaly, Chapter III). Sources of skeletal variation can either manifest through intrinsic processes (e.g., caused by variation in developmental processes and timing or genomic expression) or interactions of morphology with extrinsic factors (e.g., plasticity or adaptation to mechanical loading over time). A body of literature suggests that joint articular external shape many not significantly change in response to mechanical adaptation over an individual's lifetime (Auerbach & Ruff, 2006; Lazenby, Cooper, Angus, & Hallgrímsson, 2008; Ruff, 1994, 2002) as do other parts of long bones, suggesting much of joint shape variation is established during growth and development. This results in adult joint shape patterns that include more

morphological variance in the concave articular surface relative to their convex counterparts, more variation in joints with higher ranges of motion, and higher articular surface shape covariance in joints with complex morphologies (Horbaly et al., Chapter II; Horbaly, Chapter III). Given the high incidence of joint disease in humans—and subsequently, the interest of clinicians in treating departures from good joint health—it is important to establish whether variation in articular surface shape patterns inform differential onset and progression of joint disease within a population. A growing literature has begun to identify a shape component to joint disease (Gregory et al., 2007; Haverkamp, Schiphof, Bierma-Zeinstra, Weinans, & Waarsing, 2011; Lynch et al., 2009; Morales Martinez et al., 2020; Wise et al., 2018), yet the local shape variation driving this relationship remain elusive. This study investigates local differences in joint shape in a population of contemporary individuals with knee replacements relative to a “healthy” sample to determine: 1) whether group differences exist, and 2) which aspects of shape drive any observed differences.

Rheumatic diseases attack the bones, joints, and connective tissues of the human skeleton. A major subgroup of rheumatic diseases that localize to the joints are commonly referred to as arthritis. The Centers for Disease Control reports that osteoarthritis (OA) is the most common of these rheumatic diseases, accounting for over 32 million arthritis cases (Barbour, Helmick, Boring, & Brady, 2017), or one in four American adults diagnosed with arthritis (approximately 58.4 million people). Total knee arthroplasty (TKA) constitutes over half of joint replacement procedures among patients with OA who seek joint replacement (The American Joint Replacement Registry, 2020). Knee arthritis has proliferative effects, often impacting the ipsilateral hip joint (Nam, Tsai, Dimitriou, Li, & Kwon, 2016), and prevalence is only expected to increase in future decades due to increasing lifespans of aging generations and a

desire for quality of life improvements (Cram et al., 2012; Hootman, Helmick, Barbour, Theis, & Boring, 2016; Kurtz et al., 2009), making joint health a top priority for the healthcare industry. Onset and progression of knee OA is often associated with biomechanical factors, which can be influenced by knee morphology and alignment (Brouwer et al., 2007; Sharma et al., 2010). OA diagnosis is commonly based on semi-quantitative radiographic methods that include a five-point scale assessment of cartilage loss and subsequent joint space narrowing, osteophyte presence, and subchondral features, among others (Kellgren & Lawrence, 1957). While this approach is a field-wide standard for tracking the progression of OA, it is not designed to identify proactively the features of the knee that may predispose an individual to an OA diagnosis and/or an eventual need for TKA.

Researchers have made strides in applying shape analysis to hip and knee OA research, but much of this work has been on two-dimensional shape from radiographs (Gregory et al., 2007; Haverkamp et al., 2011; Lynch et al., 2009; Wise et al., 2018). Two-dimensional shape studies can still be informative; for example, Wise et al. (2018) found that when females in their sample exhibited certain knee shapes, their risk of developing OA was lower than the general risk for women. They concluded that certain joint shapes may mitigate an individual's propensity to develop OA, but the nature of their data prevented them from stating specific aspects of joint shape that are contributing to this mitigating effect. Morales Martinez et al. (2020) used three-dimensional (3D) shape modeling approach using MRI images of the knee to determine whether bone shape exerted an effect on the presence of radiographic OA. Their analysis did not identify specific articular shape qualities that may predispose an individual to disease onset. However, they did conclude that shape can be used as a predictive biomarker for OA development, justifying the exploration into more local features of shape that may be driving this effect.

Prior work (Horbaly et al., Chapter II) has demonstrated that greater variation in concave than convex joint surfaces may create opportunities for the concave surfaces to express variation beyond the range of variation expressed in convex surfaces, potentially resulting in a mismatch in articulating surfaces. While any mismatch may, in part, be accommodated by the presence of articular cartilage, the pattern of covariance between directly articulating joint surfaces does not align with expectations based on the amount of articular cartilage in each joint (Horbaly, Chapter III). This suggests that the lack of shape correspondence between joint surfaces may not be overcome by cartilaginous padding, and that local morphological variation could have an impact on disease outcomes.

The restriction in morphological variance exhibited by the convex articular surfaces of modern humans (Horbaly et al., Chapter II) may suggest a higher propensity for developing shape-related pathology compared to their concave counterparts. Presumably, the variance distributions produced by Horbaly et al. (Chapter II) represent “healthy” joint tolerances, of which the convex articulations exhibit a much narrower range. Alterations to this morphologically restricted surface may fall outside this presumably healthy range, resulting in pathological conditions. Likewise, the high variance observed in concave surfaces indicates a tolerance for a larger range of morphologies to be present and functional. Thus, I hypothesize that the distal femora of individuals needing TKA will exhibit shape differences that make them clearly distinguishable from a non-TKA population due to the narrow range of variation a non-TKA receiving population occupies; further, I expect specific identifiable portions of the distal femoral articular surface to drive this difference in TKA vs. non-TKA groups. This paper will use three-dimensional geometric morphometrics to explore local shape variation that may

differentiate between individuals in the TKA receiving population and those who did not receive arthroplasty.

Materials and Methods

Forty-seven adult skeletons from the Bass Donated Skeletal Collection at the University of Tennessee were examined: twelve (the TKA group) who were the recipients of unilateral TKA and had antimeres that exhibited no macroscopic signs of pathology (e.g., lipping of articular surfaces, eburnation, bone erosion); and 35 individuals (the non-TKA group) with no knee replacements or signs of pathology. Individuals in the non-TKA group were selected to reflect near-identical sex ratios and age ranges to the TKA group, and therefore was not a random sample. Demographic summaries of the non-TKA and TKA individuals are provided in Tables III.1 and III.2, including stature and weight that were available for most individuals in the sample.

Fourteen 3D landmarks were collected using an Immersion Microscribe GX2 on the distal articular surface of all bony femora (i.e., both left and right sides for the non-TKA sample, when possible, and on the un-replaced knee of TKA individuals). Landmarks were selected to approximate the major features of the femoral articular border, including points of greatest projection and curve inflection. Individual landmark definitions are provided in Table III.3 and Figure III.1. All landmark data were subjected to a full Procrustes transformation using the ‘geomorph’ package (Adams, Collyer, Kaliontzopoulou, & Baken, 2021; Baken, Collyer, Kaliontzopoulou, & Adams, 2021) prior to statistical analyses. Prior research (Grelsamer, Dubey, & Weinstein, 2005; Horbaly et al., Chapter II) indicated no significant differences in morphological variance between male and female distal femora using Procrustes-transformed

landmarks, thus sexes were pooled for all analyses. Analyses were conducted within-sides due to half of the TKA sample exhibiting right-side replacements and half left-side replacements, though laterality is not expected to produce significant differences to the results due to prior findings that left and right articulations exhibit consistent variance structures (Horbaly et al., Chapter II).

Statistical analyses

Statistical analyses were conducted in R (R Core Team, 2021) and designed to explore various comparisons among the distal femora of the non-TKA sample and unreplaced distal femora of individuals who received a unilateral TKA. Principal components (PC) analyses were used to explore whether the shape of distal femora among individuals with unilateral TKA have distinctive shape from the femora of individuals who have never received a knee replacement. PC scores were compared to living stature and weight data for the sample using a combination of Pearson correlations and canonical correlation analysis (CCA), the latter showing the relationship between PC shape matrices while accounting for any collinearity relationships within each. Student's *t*-tests were conducted to test for significant relationships between donor stature, weight, and TKA status.

Results

Principal components plots demonstrate that distal femora of most TKA individuals are distinguishable from those of non-TKA individuals (Figures III.2 and III.3). The first principal component for left knees explains more of the variance than the first principal component of right knees. Conversely, PC2 in right knees describes more of the variance in the right-side

sample than the left side PC2 does for left knees. Wireframes were created for the morphologies at the extremes of the PCA plot to better visualize the changes in shape that occur across PC1.

Shape changes along PC1 indicate a difference in condylar curvatures in the anteroposterior direction in TKA individuals. These differences are most evident in medial condylar landmarks 4 and 5, which exhibit more medial and anterior placement, respectively, than in the non-TKA group (see Figures III.1 and III.2). The apex of the curve of the medial condyle articular surface occurs more anteriorly in the TKA distal femora. From the posterior perspective, the medial condyle also exhibits the most conspicuous contrast in shape compared to the non-TKA group; landmarks indicate a slight medial rotation of the posterior portion of the medial condyle (Figures III.2 and III.3). The posterior aspect of the lateral condyle in TKA individuals is similar in shape to that in the non-TKA group but is shifted laterally.

Pearson correlations indicate that PC1 scores are not significantly correlated with stature or weight for either left or right knees (Table III.4). These results are corroborated by the CCA results in Table III.5. Canonical correlations between PC scores and stature and weight are low; dimension 1 explains only 40% of the correspondence between the two datasets. PC1 and PC2 are more strongly correlated with CCA dimensions 1 and 2 than either stature or weight are with the CCA dimensions.

Discussion

Prior studies have established associations between both 2D and 3D joint shape data and osteoarthritis, yet specific shape qualities that drive these relationships remain elusive. The shape of the femoral condyles, which was indicated to have less variance than the proximal tibia (Horbaly et al., Chapter II) and thus potentially lower tolerance for higher variation in shape,

appears to distinguish between individuals who received TKA and those who did not in an age- and sex-matched sample, as hypothesized. Most of these morphological distinctions occur in the medial condyle, with the notable medial displacement of the lateral condyle relative to the medial condyle in the non-TKA group.

Given that the sample selection process confirmed the knees of TKA individuals did not exhibit obvious macroscopic changes associated with osteoarthritis, the shape differences observed here are not due to pathological remodeling of the bone. As noted, because the two sample groups were sex- and age-matched, these factors did not motivate the variation along PC1 and PC2, either. The effect of body mass on morphology, which is normally associated with PC1, is likely not driving the distinctions in medial condyle morphology between the groups because of the use of Procrustes transformation, though it is notable that the TKA group were significantly more massive than the non-TKA group (Table III.1). Pearson and canonical correlations corroborate that neither the changes along PC1 and PC2 nor an individual's replacement status are explained by donor stature or body mass.

While the shape differences reported about the medial condyle in the Results cannot be directly linked to pathology or the need for TKA with the available data, a review of the literature shows consistencies between the shape differences presented here and clinical observations. During stance phase of a normal gait cycle, higher loading forces are transmitted through the medial, rather than lateral, side of the tibiofemoral joint (Andriacchi, 1994; Brouwer et al., 2007; Morrison, 1970), which predisposes the medial condyle to biomechanically induced OA. In a study that analyzed wear patterns of the distal femur in individuals undergoing TKA surgery for OA, Weidow, Pak, and Kärrholm (2002) observed a pattern of greater degeneration on the medial condyle than the lateral condyle, consistent with this medialized axis of peak

loading; this corroborates other studies focusing on wear patterns of the distal femur. The anterior portion of the medial condyle, specifically, showed greater cartilage degeneration than it did posteriorly; the lateral condyle exhibited the opposite wear pattern (Weidow et al., 2002). The results of the present study show an anterior shift of the medialmost landmark on the medial condyle, which may be linked to greater cartilage degeneration on the medial condyle of TKA individuals.

Though the association between morphology and soft tissue wear within the knee could not be assessed due to the lack of observable cartilage, bony morphology alone may play a role in the eventual degeneration of the joint. Wear caused by an altered axis of typical biomechanical loading may result from the morphological variant highlighted in comparing the medial condyle shape between a TKA-receiving and non-TKA sample. This effect is evident when individuals exhibit variation in the angle between their femur and tibia as well – individuals presenting with either varus or valgus alignment are more likely to experience OA progression (Brouwer et al., 2007; Sharma et al., 2010). Alternatively, innate femur morphology may not be symptomatic until gait is altered by the presence of joint disease or TKA hardware in the opposing knee, forming a feedback loop and causing the antimeres to progress toward OA. Whether joint shape is causal of OA or purely a response to OA should be teased apart in future studies.

The fact that distal femur shape differences can be observed, even in a small sample of TKA individuals, is perhaps expected due to prior work demonstrating the limited morphological variation in convex articular surfaces (Horbaly et al., Chapter II). Though it is unknown precisely where the TKA individuals in the present sample fall relative to the femoral variance distributions from Horbaly et al. (Chapter II), Horbaly et al. did pre-screen and exclude skeletons exhibiting macroscopic signs of OA. It is possible their sample inadvertently included skeletons

with pre-osteoarthritic morphologies (i.e., individuals with shapes similar to the TKA individuals but who died prior to pathological onset and/or the need for TKA); however, this may only have been a small subset of their total sample which ultimately converged on a pattern of highly restricted distal femoral morphology. This high degree of shape restriction results in identifiable shape differences (such as those observed presently in the TKA group) in contrast to the non-TKA group; furthermore, as the variance distributions produced by Horbaly et al. (Chapter II) may approximate the healthy range of shape tolerances in a population, the significant deviation from the non-TKA group observed by the present TKA sample may indicate their distal femoral fall toward the extremes or wholly outside standard variance ranges.

Future work should include 3D landmarks of the proximal tibiae from TKA individuals to determine whether associated changes are also occurring there. Longitudinal studies that follow individuals prior to and throughout an osteoarthritis diagnosis would be helpful in determining whether the shape alteration leads to disease or the reverse. This would also assist in tracking whether shape differences occur as a function of time-since-replacement, a piece of information that is rarely documented in the self-reported voluntary body donation packets associated with the present sample.

Conclusion

This paper contributes to existing literature that indicates a portion of the population may be morphologically predisposed to developing OA and require a subsequent knee replacement. These differences cannot be explained by any of the demographic attributes of this sample. The present results add to existing literature by identifying local three-dimensional aspects of shape that apparently drive much of the shape differences between TKA and non-TKA individuals, and

directly aligns these local shape features with evidence of increased degeneration in the clinical literature. In addition to the medial rotation of the posterior portion of the medial condyle, the medial curvature of the medial femoral condyle occurs more anteriorly in individuals needing TKA; this is consistent with the region of greatest degeneration on the anterior portion of the medial condyle. Future studies should consider these shape features and clinical observations in tandem with genetic data that may bring us closer to developing a diagnostic process for identifying osteoarthritis-prone individuals based on skeletal morphology.

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APPENDIX III

Table III.1: Summary of demographic breakdown for left side sample of non-TKA and TKA individuals

	Min.	1 st Qu.	Median	Mean	3 rd Qu.	Max
<i>Non-TKA (n = 31)</i>						
Age	49	65	73	73.32	82	91
Stature (cm)	147.3	160.0	167.6	169.2	178.4	193.0
Weight (lbs)	105.0	128.5	142.5	156.0	166.5	280
<i>TKA (n = 6)</i>						
Age	49	69.25	74	72.83	82.50	87
Stature	160.0	172.7	175.3	176.8	188.0	188.0
Weight	127.0	166.5	188.0	187.7	220.0	233.0

Table III.2: Summary of demographic breakdown for right side sample of non-TKA and TKA individuals

	Min.	1 st Qu.	Median	Mean	3 rd Qu.	Max
<i>Non-TKA (n = 33)</i>						
Age	49	65	73	73.88	81	91
Stature (cm)	149.9	162.6	170.2	170.1	177.8	193.0
Weight (lbs)	90	131.2	145.0	157.0	180.8	280
<i>TKA (n = 6)</i>						
Age	49	69.25	74	72.83	82.50	87
Stature	160.0	172.7	175.3	176.8	188.0	188.0
Weight	127.0	166.5	188.0	187.7	220.0	233.0

Table III.3: Distal femur landmark definitions

LM #	Location	Description
1	Patellar surface	When viewed distally, the anteriormost projection of the lateral patellar lip
2	Lateral condyle	When viewed distally, the lateralmost projection of the lateral condyle
3	Lateral condyle	When viewed distally, the posteriormost projection of the lateral condyle
4	Patellar surface	When viewed distally, the anteriormost projection of the medial patellar lip
5	Medial condyle	When viewed distally, the medialmost projection of the medial condyle
6	Medial condyle	When viewed distally, the posteriormost projection of the medial condyle
7	Medial condyle	When viewed posteriorly, the superiormost projection of the medial condyle
8	Medial condyle	When viewed posteriorly, the medialmost projection of the medial condyle
9	Medial condyle	When viewed posteriorly, the lateralmost projection of the medial condyle
10	Medial condyle	When viewed posteriorly, the inferiormost projection of the medial condyle
11	Lateral condyle	When viewed posteriorly, the superiormost projection of the lateral condyle
12	Lateral condyle	When viewed posteriorly, the medialmost projection of the lateral condyle
13	Lateral condyle	When viewed posteriorly, the lateralmost projection of the lateral condyle
14	Lateral condyle	When viewed posteriorly, the inferiormost projection of the lateral condyle

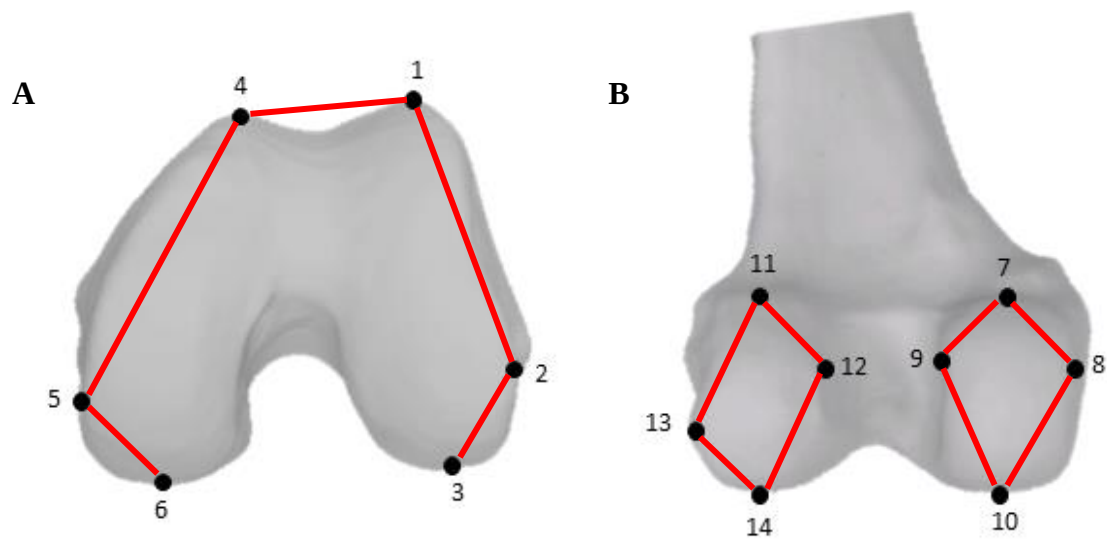


Figure III.1: Distal femur landmarks; distal view (A); posterior view (B). Red lines indicate wireframe template.

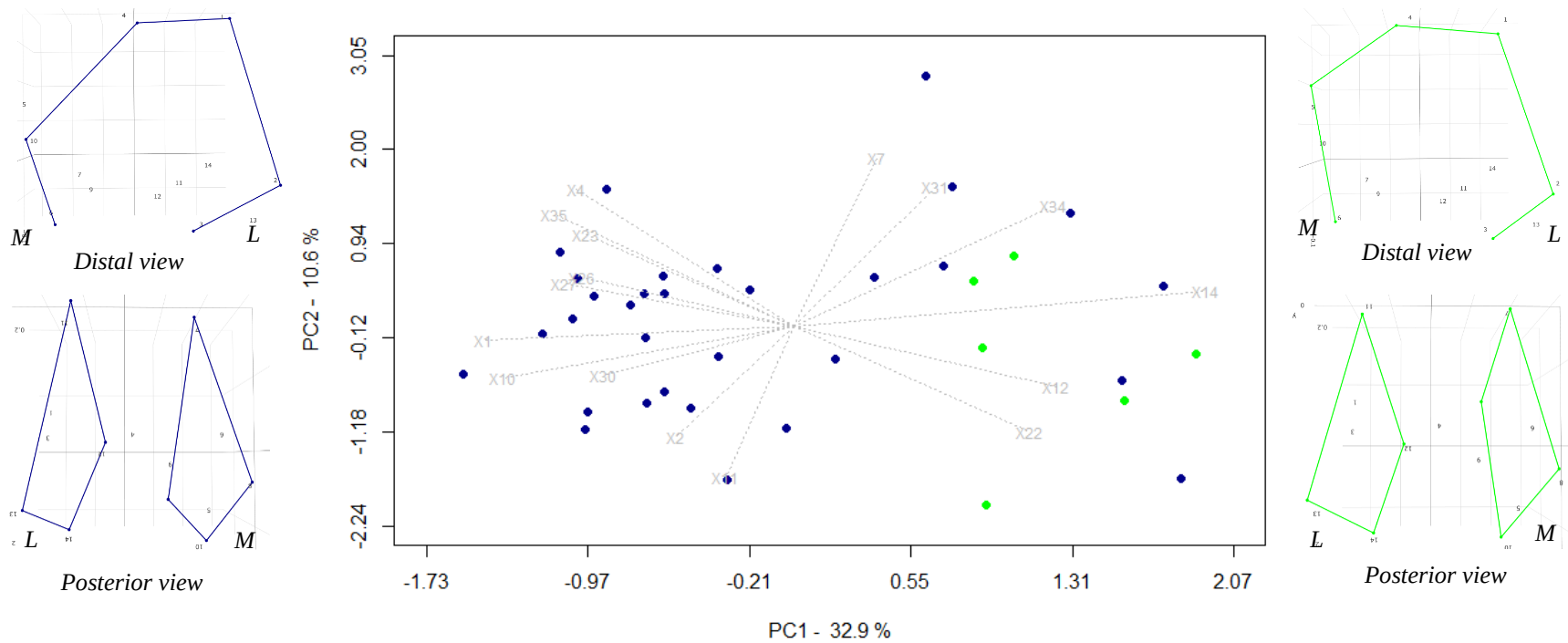


Figure III.2: Principal components analysis for left femora of non-TKA and TKA groups. Wireframes reflect the distal and posterior femur shape changes from left to right along PC1, and medial and lateral directions are indicated by ‘M’ and ‘L,’ respectively. Blue color indicates non-TKA individuals; green indicates TKA individuals.

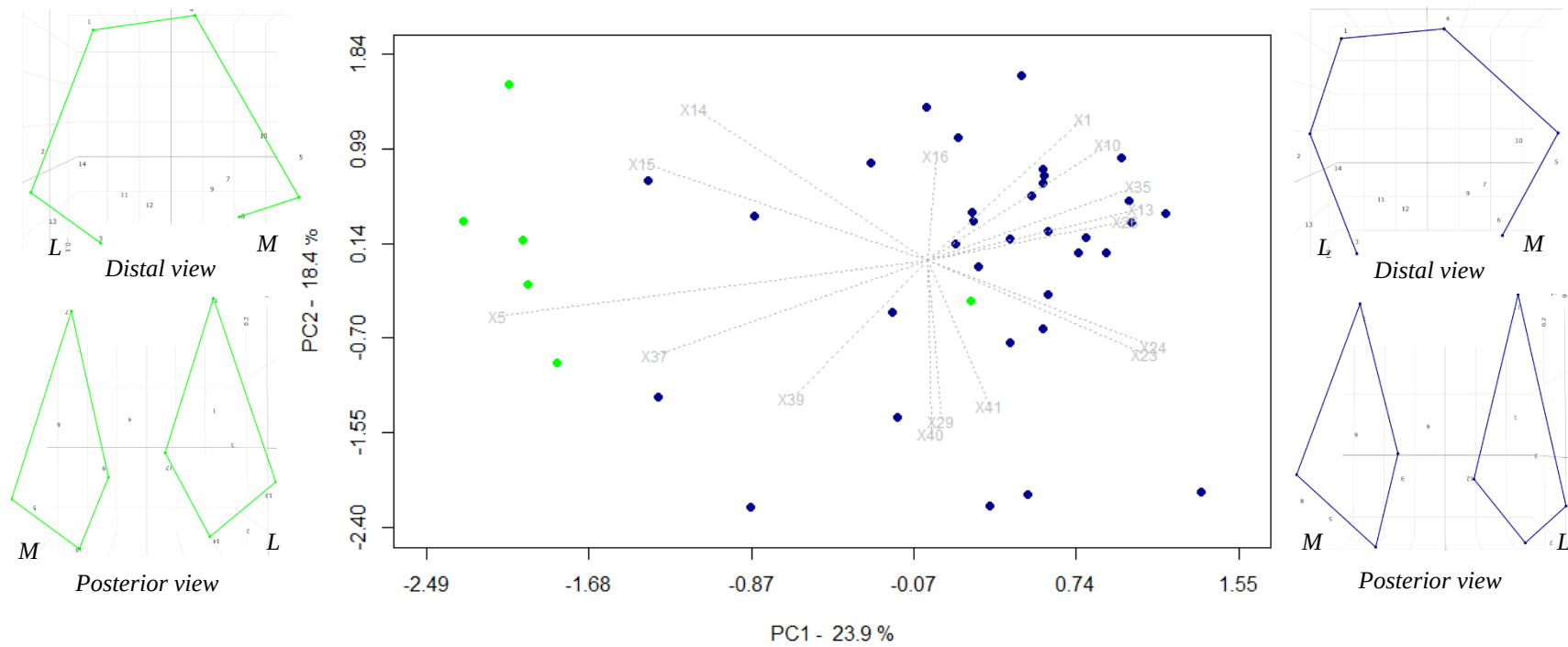


Figure III.3: Principal components analysis for right femora of non-TKA and TKA groups. Wireframes reflect the distal and posterior femur shape changes from left to right along PC 1, and medial and lateral directions are indicated by 'M' and 'L,' respectively. Blue color indicates non-TKA individuals; green indicates TKA individuals.

Table III.4: Pearson correlation values between donor stature, weight, and principal component scores 1 and 2

Pearson correlations	<i>t</i>	df	<i>p</i> -value
Stature ~ PC 1	1.78	27	0.09
Weight ~ PC 1	1.65	26	0.11
Stature ~ PC 2	1.29	27	0.21
Weight ~ PC 2	0.53	26	0.60

Table III.5: Canonical correlation results between donor stature, weight, and principal component scores 1 and 2

	Dimension 1	Dimension 2
Canonical correlation	0.40	0.11
<i>PC Score coefficients</i>		
PC1	0.17	-0.10
PC2	0.08	0.16
<i>Donor data</i>		
Stature	0.01	0.01
Weight	0.00	-0.01

Table III.6: Two sample t-tests for significant relationships between and individual's TKA status and their stature and weight

T-tests	<i>t</i>	df	<i>p</i> -value
TKA status ~ stature	-1.32	5.85	0.24
TKA status ~ weight	-1.65	8.43	0.13

CHAPTER V: CONCLUSIONS, IMPLICATIONS, AND FUTURE RESEARCH

The collection of studies presented in this dissertation take a comprehensive look at articular surface morphology by establishing the magnitude and distribution of variation shape, evaluating the covariance between surfaces relative to their complementary and/or analogous function, and exploring whether variation in articular morphology relates to joint replacement status. By taking a geometric morphometric approach, this dissertation added to our previous understanding of joint variation, which had largely been established by studies focusing on linear dimensions. Five main findings were established by this dissertation:

1. Convex articulations are extremely limited in variation relative to the consistently higher variance in concave surfaces (Chapter II).
2. Variance in articular surface shape, using Procrustes-transformed landmarks, is not statistically different between antimeres or females and males (Chapter II).
3. High range of motion joints exhibit greater morphological variation (Chapter II).
4. Both complementary and analogous function promote covariance between articulations; however, analogous function of the humerus and femur is the strongest covariance relationship (Chapter III).
5. Individuals who exhibit specific local shape variations of their distal femur are more likely to have received a knee replacement during life (Chapter IV).

How these findings relate to current and future literature are explored below, followed by a discussion of limitations and future directions.

Differential Variance in Convex and Concave Articular Morphology

An analysis of variation within and among the major synovial joints of the human limb reveals previously unknown patterns of morphological variance. The most striking pattern to emerge is the difference in variance observed between the convex and concave components of each joint. It was predicted that, because complementary articulations must grow and function in tandem with one another to maintain integrity of the joint, their propensities for displaying variance would be consistent with one another and across the population. However, the results of Chapter II demonstrate that within each joint, the concave surface exhibits significantly greater morphological variance across individuals than the convex surface, pointing to the possibility that morphogenic processes are not entirely consistent between articulating surfaces, despite their spatial proximity and complementary function.

From a macroscopic perspective, prior research has pointed to differences in functional roles between the two joint faces. Hamrick (1996) studied articular curvatures in strepsirrhine primates of varied locomotion styles and found the concave curvature to be indicative of multidirectional joint stability while the convex contour relates to the joint's range of motion. It is possible this partitioning of functional roles between the two surfaces may result in differential selective pressures—if joint range of motion must be relatively consistent among all individuals to ensure proper function, and range of motion is dictated by the convex surface, then it stands to reason that this surface would be more tightly regulated and thus more limited in shape variation across a population. If regulatory developmental factors are focused on the morphologically consistent convex surface, it is possible that the concave surface forms *in response to* the active determinants of its convex counterpart; in other words, the concave surface may form in reaction

to the processes driving the convex morphogenesis, and thus are less directly regulated and more likely to exhibit morphological variation across a population.

Pacifici, Koyama, and Iwamoto (2005) explored three possible models for convex/concave morphogenesis. The models proposed were: 1) growth of the convex surface would protrude into the concave surface; 2) the concave surface grows around the convex surface; or 3) a combination of these two models occur in tandem. The first scenario would most closely align with the above prediction that the concave surface forms as a reactive response to active morphogenesis in the convex surface. Yet, Pacifici et al. assert that, based on their experimental research, the third combinatory scenario is the most likely given the patterns of cell proliferation and gene expression they observed in chick embryos. If both the convex and concave surface are actively growing in concert with one another, rather than the concave surface responding to growth in the convex surface, there may still be cellular processes or regulatory mechanisms specific to each component that allow shape to vary more freely in the concave surface.

In the same study, Pacifici et al. (2005) monitored the distribution of *GDF5* (as reviewed in Chapter II, a growth factor heavily involved in the development of synovial cavity structures) during development of chick interphalangeal joints. They found that, during a specific phase in development, *GDF5* ceases to be evenly distributed throughout the interzone and instead is limited in expression to the developing convex surface. *GDF5* is known to play a large role in establishment of the interzone, joint morphogenesis, and genesis of future joint structures such as the synovial cavity and connective tissues (Chijimatsu & Saito, 2019; Pacifici et al., 2005; Towers & Tickle, 2009a, 2009b). It is possible that the high concentration of *GDF-5* signals a more robust developmental network occurring at the convex surface that is somehow limiting its

ability to accrue variation. Indeed, a more complex feedback loop has been associated with a reduction in phenotypic variability due to the network's robustness against perturbations during development (Sears, 2014). The absence of *GDF5* on the concave surface during certain developmental phases gives further evidence of a different developmental genetic network in concave and convex surfaces after initial formation, which may permit more variation to accrue over development for concave articulations. Without a developmental model, however, it is uncertain when during joint formation the differences in variance between concave and convex surfaces manifest, and if they elaborate over the course of ontogeny. Future experimental studies testing this hypothesis could directly link the findings in Chapter II with the developmental differences that appear to occur between the convex and concave articular components.

Chapter II also considers potential differences in joint variation between the sexes, given that sexual dimorphism is one of the most conspicuous sources of biological variation in any species. Variance was assessed based on trace values of the variance-covariance matrices for each joint and articular surface. No significant differences in articular variance are observed between the sexes. Often-cited locations of joint-specific dimorphism include the carrying and quadriceps angles of the elbow and knee, respectively, though whether these locations consistently exhibit dimorphism is controversial (Grelsamer, Dubey, & Weinstein, 2005; Kazi, Keche, Joshi, & Wanjari, 2017; Kothapalli, Murudkar, & Seerla, 2013; Kumar et al., 2010; Ruparelia, Patel, Zalawadia, Shah, & Patel, 2010; Sharma, Jabeen, Magotra, & Choudhary, 2019), with many of the observed differences appearing to more closely align with body size than sex (Grelsamer et al., 2005). While human sexual size dimorphism does occur to some extent—males are on average 15% heavier and 9% taller than females (Stulp & Barrett, 2014)—there is a significant amount of overlap in human body size. The joint shape data collected for

this dissertation were subjected to a full Procrustes transformation, minimizing the influence of size. Therefore, the present results suggest that shape differences between males and females do not present a significant difference in variance structure around the mean.

Finally, variance patterns were predicted to exhibit a relationship to range of motion, whereby joints with reduced range of motion would need to meet fewer functional demands and have greater leeway for accruing variation in a population. Results of Chapter II reveal the opposite pattern to be true: joints with greater range of motion (shoulder, hip) exhibit greater morphological variation. It is possible this pattern is more reflective of the type of joint architecture required for range of motion rather than the range of motion itself. The morphology of high range of motion joints is predicated on a singular requirement of topographical simplicity that produces no morphological impediments to multidirectional movement. Low range of motion joints, on the other hand, must limit movement in many directions to ensure multiplanar stability *as well as* full ranges of motion in their planes of movement. These morphological limitations to movement must be relatively consistent among individuals in a population to provide comparable ranges of motion. It is possible the stricter shape requirements for low range of motion joints places tighter restrictions on their ability to vary.

The results also indicate a reduction in articular variation from proximal to distal elements within a limb. This runs counter to the proposed phenomenon that variation accumulates in more distal limb segments (Buck, Stock, & Foley, 2010; Holliday & Ruff, 2001), presumably due to differential functional adaptation and/or the additive effects of variance-generating processes as the limb develops proximal to distal. Evidence does exist to support the opposite—that distal limb segments show reduced variation (Shaw, Stock, Davies, & Ryan, 2014; Stock, 2006), perhaps in response to tissue economy in distal elements—and the results of

this present study support this latter pattern, though the inclusion of the distalmost limb joints of the wrist and elbow should be included in future studies to determine whether the pattern is conclusive for this sample.

The patterns of variance elucidated in Chapter II may point to differences in the underlying mechanisms of morphogenesis between convex and concave surfaces, and the relationship between topographical complexity and shape variance. While much of the joint morphogenic process remains to be described, the findings of this dissertation offer a potential avenue of future research that could connect what is currently known about developmental networks, their relationship to morphological variance, and the patterns of shape variation observed in Chapter II.

Covariance Between Surfaces of Complementary vs Analogous Function

An analysis of covariance structure within and among joints revealed different relationships between surfaces that are complementary for function (directly articulating with one another), and analogous for function (performing the same role for the upper or lower limb). All directly articulating surfaces show significant covariation; this result was consistent with predictions that hypothesized articulating shapes would need to covary to achieve semi-conformity for the purposes of joint function. It was anticipated that covariance would exhibit an inverse relationship with the amount of cartilage present—low cartilage joints would require more conformity from the bony components, while high cartilage joints would accommodate for articular shapes that were not as conformed. Interestingly, the hierarchy of the covariance relationships ran counter to this expectation. Though the elbow—the joint with the least amount

of cartilage—did indeed exhibit the strongest covariance, it was followed by the knee, the shoulder, and then the hip. Given this reversal of expectations (except for the elbow, which behaved as expected with the highest covariance value), it may suggest that the amount of articular cartilage present at the joint is not necessarily related to the degree of covariance between articular shapes. As explained in Chapter I and reviewed above, the specific details of development in articular surfaces await further study, but research has shown that the onset of morphogenesis (shaping of articulating joint surfaces) occurs before the appearance of synovial cavity structures such as specialized cartilages, fluid, and ligaments (Chijimatsu & Saito, 2019; Pacifici et al., 2005; Pacifici et al., 2006). Due to cartilage appearing later in the developmental process, its reciprocal influence with the shape of the joint may be limited. As was described in Chapter III, it is possible that the hierarchy of covariance, then, is more reflective of joint function than cartilage presence. The joints with more complex morphologies are also those that have more restricted ranges of motion, and it is the more intricate joint morphology that contributes to limiting movement in certain planes and thus less tolerance for independent variation in these surfaces.

The hierarchy of covariance does, however, relate to the variance distributions from Chapter II. The elbow and knee showed less disparity in variance distributions of their articular surfaces and thus showed greater covariance; the shoulder and hip had more difference in variance distributions between their concave and convex surfaces due to the high amount of morphological variation observed in their respective concave surfaces. It is possible that the significant mismatch between the articular distributions of the shoulder and hip have implications for joint injury or degeneration; a more detailed discussion of the clinical implications of joint shape is provided in the next section.

Fewer significant covariance values were observed when comparing functional analogs, but the relationships that were significant (proximal and distal humerus and femur) showed stronger associations than directly articulating morphologies. This may reflect their additional serially homologous relationship and may indicate that functional relationships alone are not enough to promote strong covariance between articular surfaces. This is borne out by the lack of significant covariance relationships observed between the proximal ulna and proximal tibia, a pairing that solely represents functional analogy as they are the major concave components of their respective hinge joints and are not serially homologous with one another (Fraser & Robarts, 1914; Lewin, Opitz, & Reynolds, 1986; Martínez-Frías, Frías, & Opitz, 1998; Winter, 1988). The girdle elements of scapula and os coxa also do not exhibit significant covariance between their articular surfaces, which may be reflective of their reduction in integration in tetrapods over evolutionary time and their distinct embryological tissue origins (Kardong, 1997; Pellegrini, Pantano, Fumi, Lucchini, & Forabosco, 2001; Sears, Capellini, & Diogo, 2015; Young, 2004).

Some of the covariance relationships observed in Chapter III are notably strong, particularly between the humerus and the femur. The strength of this covariance between functional analogs (and serial homologues), prompts a consideration of morphological integration. Integration refers to the emergent covariance between phenotypic traits that belong to the same functional complex or that share some combination of underlying factors involved in growth and development (Cheverud, 1996; Frost, 1979; Hallgrímsson, Willmore, & Hall, 2002; Hamrick, 1999; Klingenberg, 2008, 2009; Pavlicev, Cheverud, & Wagner, 2009). Due to the accessibility of the phenotype and its tendency to approximate correlated variation as predicted by the genotype (Cheverud, 1988; Sadini, Kemper, Wray, & Trzaskowski, 2018), integration is a useful framework for analyzing genetic associations between morphological skeletal

characteristics. Specifically, researchers examining integration between upper and lower limb elements have demonstrated that divergences and specializations, and thus lower integration between elements, relate to functional adaptation (Rolian, 2009; Sylvester, 2006; Young, Wagner, & Hallgrímsson, 2010). Species that exhibit uniformity of function between fore- and hindlimbs (such as quadrupedal species) have high limb integration while humans, among the most extreme in their limb functional divergence, have lower integration between limbs. While integration is predominantly identified through trait covariance, covariance is not equivalent for integration without an evolutionary model (Hansen and Houle, 2008; Hallgrímsson et al., 2009). Therefore, while morphological relatedness has been tested here with covariances, any interpretation of integration should be conservatively applied. The results of this dissertation provide evidence that the proximal and distal humerus and femur articular morphologies are strong candidates for integration, and future studies should include tests of integration and evolvability to elucidate this relationship further.

Clinical Implications of Joint Shape Variation in the Knee

Chapter IV contributes to an existing literature that points to the likelihood that certain joint morphologies may have a relationship to pathogenesis or disease status (Gregory et al., 2007; Haverkamp, Schiphof, Bierma-Zeinstra, Weinans, & Waarsing, 2011; Lynch et al., 2009; Morales Martinez et al., 2020; Wise et al., 2018), and advances our understanding of the local joint features that may be driving this relationship. Individuals who received a total knee arthroplasty exhibit two distinct differences related to their medial femoral condyles: anterior shift of the medial curvature, and medial rotation of the posterior condylar surface. While longitudinal tracking of individuals exhibiting this articular shape would be required to

determine the direct effect on pathological progression, clinical literature does point to the anterior portion of the medial condyle as a high-wear location in individuals requiring TKA (Weidow, Pak, & Kärrholm, 2002).

It is unclear how individuals exhibiting the TKA-related medial condylar variation relate to the variance distributions as presented in Chapter II. One of the questions arising from the results of Chapter II is whether individuals who develop joint disease fall at either extrema of the concave surface distribution, which across the board has more variance than the complementary convex surface. It is possible individuals who develop joint disease exhibit joint shapes that fall entirely *outside* of the distributions observed here given that the criteria for the Chapters II & III samples excluded individuals with signs of osteoarthritis, lipping, or any other joint degeneration. However, considering the high national prevalence of osteoarthritis and the large sample size of 200 individuals used in Chapters II & III, it is possible—and perhaps likely—that an unknown subset of the sample could have been pre-osteoarthritic (i.e., they died prior to manifestation of the disease), and exhibit shape features similar to the TKA individuals in Chapter IV. Because it is impossible to know, especially from macroscopic assessment, whether a skeletonized individual *would have* developed osteoarthritis had they lived longer, it would be conservative to assume that the variance distributions produced in Chapter II did indeed include pre-osteoarthritic individuals. Therefore, it can be reasonably hypothesized that those morphologies do fall toward the extrema of the distributions rather than wholly outside them, though this requires a direct test.

Nonetheless, the variance distributions elucidated in Chapter II point to the potential for mismatch between the convex and concave articular surfaces given the differential patterns of variation. For convex surfaces, all individuals in the sample cluster tightly around the mean

morphology, while there is significantly more spread in their complementary concave articulations. The higher the disparity in these distributions, the lower the covariance between articular surfaces (Chapter III). Though future work should analyze the exact shape changes occurring across the distributions, it may be that the disparity in variance results in suboptimal shape matches between convex and concave components. Even if the mismatch is slight, it might be enough to cause altered gait or biomechanical loading which can lead to joint degeneration (Brandt, Myers, Burr, & Albrecht, 1991; Kippel & Dieppe, 1994; Stone & Yu, 1997; von Eisenhart-Rothe et al., 1997).

Considerations for Response to Load: Chondral Modeling and Functional Adaptation

In the Introduction of this dissertation (Chapter I) I introduce various phenomena describing the formation and response of articular bone to biomechanical loading. The most comprehensive model to date to describe joint shape formation is the chondral modeling theory (Frost, 1979; Hamrick, 1999; Plochocki, Ward, & Smith, 2009), though conclusive evidence that this model accurately depicts all bone modeling from hydrostatic pressure is mixed (Congdon, Hammond, & Ravosa, 2012; Hammond, Ning, Ward, & Ravosa, 2010). While this dissertation did not directly observe cellular modeling processes of the articular surfaces, much of the evidence in support of chondral modeling comes from macroscopic observations of bone (e.g., Plochocki et al., 2009; Sylvester, 2015). If chondral modeling is an accurate representation of the processes of joint shape formation during postnatal growth, then the results of Chapter II indicate that, despite experiencing equal hydrostatic pressures as part of the same joint capsule, convex and concave articulating surfaces have differing abilities to respond to those pressures via

chondral modeling. The relatively invariable convex surface may experience stronger regulatory mechanisms that limit its expansion in the face of reduced hydrostatic pressure, and thus, limits opportunities for new growth and accrual of variation across the population. With one joint component being restricted, the articulating component logically must exhibit enhanced flexibility; thus, the greater variation observed in concave articular shapes may be indicative of relaxed regulatory mechanisms and a greater propensity for chondral modeling response. Collectively, this points to a model of joint morphogenesis where the more limited convex surface leads or dictates the response of the more adaptive concave surface that accommodates for the morphological restrictions of its partner.

The hypothesis of diminished response in the convex surface may contradict observations by Plochocki et al. (2009) using their *in silico* model of chondral modeling, however. In their optimal model that simulates differential hydrostatic pressure over a finite element surface, they found that greater shape change was observed in the distal femur than in the tibial condyles; the tibia (the concave surface) exhibited only minor changes. They suggested this is due to the relatively flat appearance of the tibial condyles resulting in stress gradients being distributed more efficiently across the articulations. Their optimal model also indicated that the tibia did not experience large loads per unit area and thus exhibited limited chondral modeling-related shape change (Plochocki et al., 2009).

This finding seemingly contradicts expectations based on morphological variation, yet this discrepancy may be due to the starting parameters of their computational model. Plochocki et al. (2009) base their starting morphology and finite element model on an MRI of a twelve-year-old male. Osteological growth references state that the articular surface of the proximal tibial epiphysis has “assumed its adult sellar shape” (Schaefer, Black, & Scheuer, 2009; Scheuer

& Black, 2004) by the onset of puberty, which ranges from ten to twelve years of age in males (Lee, Guo, & Kulin, 2001; Rogers, 2009). It is possible that, over the entirety of postnatal growth during which time chondral modeling is acting on the articular surfaces, the concave surface exhibits greater shape change than the convex surface, but once this is largely established by twelve years old and beyond—the time period simulated by Plochocki et al. (2009)—the tibial condyles exhibit minimal shape change. The tibia is known to exhibit a more consistent rate of growth in advance of puberty, while the femoral growth trajectory is slow pre-puberty and is followed by an increased rate of growth after pubertal onset (Scheuer & Black, 2004). It is possible these differential growth trajectories between the femur and tibia before and after onset of puberty explain the patterns of shape change observed by Plochocki et al. (2009), which may not be representative of the entirety of postnatal articular modeling.

Prior work (Congdon et al., 2012; Hammond et al., 2010) has demonstrated that expectations from chondral modeling do not appear to explain the patterns observed at all cartilage locations of a growing bone, therefore it is conceivable that this heterogeneity in cartilage behavior depending on location may also have a temporal component. In other words, a snapshot of articular modeling after the onset of puberty may not be characteristic of the broader morphological trends occurring all throughout postnatal growth. If this is the case, the accumulation of variance in the concave articular surface may not contradict the limited growth in the concave surface observed in Plochocki et al. if tibial condyle growth had occurred prior to the starting point of Plochocki and colleagues' model.

After postnatal growth, biomechanical loads affect skeletal change via bone functional adaptation (Carter & Orr, 1992; Frost, 1987; Ruff, Holt, & Trinkaus, 2006; Wolff, 1892). This remodeling response is most conspicuous at the midshaft of long bones (Macintosh et al. 2013),

as this is the location resisting the greatest bending forces during locomotion and other activities. While patterns of diaphyseal adaptation to loads are well-established (Agostini, Holt, & Relethford, 2018; Blackburn, 2011; Ingelmark, 1974; Nadell & Shaw, 2016; Plochocki, 2004; Ruff & Jones, 1981; Sakaue, 1998; Schultz, 1937; Trinkaus, Churchill, & Ruff, 1994), evidence for adaptive remodeling of the articular surface is equivocal. An existing body of work points to limited load-induced response in joint surfaces (Auerbach & Ruff, 2006; Lazenby, Cooper, Angus, & Hallgrímsson, 2008; Lieberman, Devlin, & Pearson, 2001; Ruff, 1994, 2002). Signatures of side-biased remodeling during life are heavily dependent on the repetitive activities and lifestyle of an individual, and thus, if adaptive asymmetry is occurring in the articular surfaces, I would expect a lateralized increase in articular variation across the population, given that the individuals comprising that population will adapt in ways that are specific to their “unique” lifestyle. However, the results of this dissertation demonstrate that there is no significant difference in variance between left- and right-side joints or their articular surfaces, a finding that bolsters the body of literature pointing to articular constraint (Auerbach & Ruff, 2006; Lazenby et al., 2008; Ruff, 1994, 2002). Future research on diaphyseal bone functional adaptation should compare distributions of variance for the articulations to distributions for the diaphyses to determine whether adaptation-induced asymmetry does indeed cause a shift in the distribution of variance around the mean.

Under the assumption that chondral modeling is occurring in human articular surfaces early in ontogeny and bone functional adaptation after primary growth is not, an understanding of the relationship among articular cortical bone, epiphyseal trabeculae, and biomechanical load emerges. The efficiency of articular shape for transmitting load is established early in development through morphogenic growth factors and movement in utero (Chijimatsu & Saito,

2019; Nowlan, Sharpe, Roddy, Prendergast, & Murphy, 2010; Rolfe, Shea, Singh, Bandyopadhyay, & Murphy, 2018; Shea, Rolfe, & Murphy, 2015; Singh et al., 2018), then elaborates during postnatal growth and chondral modeling (Frost, 1979; Hamrick, 1999; Plochocki et al., 2009). Once skeletal maturity is reached and chondral modeling is completed, articular surface shape reflects the (sometimes antagonistic) demands of joint function, range of motion, articular fit, and load transfer; articulations maintain this complex shape throughout adulthood barring traumatic or pathological scenarios (Auerbach & Ruff, 2006; Lazenby et al., 2008; Ruff, 1994, 2002). Flanking the fixed topography of articular cortical bone are structures with mechanisms for fine-tuning the main roles of joint morphology. Externally, cartilages accommodate for the semi-congruency of long bone ends, functioning as a labile structures that maintain a degree of articular fit even as the articular regions in contact change through joint excursion (Almajed, Hall, Gillingwater, & Alashkham, 2022; McDermott, Masouros, & Amis, 2008; Walker & Erkman, 1975). Internally, trabecular bone is free to adapt to lifestyle- or activity-specific loads through an increase in trabecular thickness or orientation (Biewener & Bertram, 1991; Fajardo & Müller, 2001; Lanyon, 1974; Rubin, Turner, Bain, Mallinckrodt, & McLeod, 2001). The remodeling of this internal architecture is not only a response to biomechanical load but is a response to that load *filtered through* the shape of the unchanging cortical morphology that has already arrived at some level of efficient force transfer during postnatal growth (chondral modeling). Because of the external chondral accommodations and the internal plasticity of trabeculae, the cortical articular shape that is formed postnatally need not anticipate *all* forms of loading that occur alter in life, but rather allow for a range of tolerances that can then be adjusted by the labile an adaptive flanking joint mechanisms. Together, these integrated systems allow for 1) modeling of the articular surface shape in response to load that

sets up the joint for load transfer during adulthood and maintains structural integrity during initial growth, 2) partial accommodation for any incongruences in the resulting bony cortical morphology via articular cartilages, and 3) internal plastic trabecular response to loading to reinforce the external architecture.

Limitations

Given the nature of the data used in this dissertation, limitations do exist. The sample consists of fully skeletonized body donors, preventing the inclusion of direct observations of the soft tissues involved in each joint. As was mentioned previously, articular cartilage exists to varying degrees in each joint capsule and serves the purpose of force distribution through the joint as well as partially accommodating for joint conformity. While effort was made to consider broad cartilaginous differences among the joints under study (e.g., how the amount of cartilage would affect joint variation and conformity), a more comprehensive soft tissue study is required to truly understand the interactions between the morphologies of the bony joint and cartilage. It is not expected that the bony morphology alone can reflect the full picture of coordinated variation within and among synovial joints.

For Chapter IV, methodological limitations exist due to sample size and data collection. As an exploratory study, only a small number of individuals with unilateral knee replacements and intact opposing knees could be landmarked, and a greater number of individuals would clarify the patterns observed in the shape differences between groups. Further, given the greater amount of error typically associated with collecting 3D landmarks using a Microscribe, a future expansion of this study should create surface models of the distal femur and place landmarks digitally.

Directly linking the femoral shape differences observed in TKA individuals (Chapter IV) to clinical and pathological outcomes would require longitudinal studies of individuals prior to and throughout disease onset and progression. Shape variation in the opposing surface of the tibial condyles should also be explored to understand the knee joint complex more holistically.

Future Research

This dissertation represents the first study to make intraspecific shape comparisons among all articular surfaces of the shoulder, elbow, hip, and knee, and the results provoke more questions to be explored in future studies. The pattern of restricted variation in convex joint shapes relative to the highly variable concave surfaces is striking, and future studies will expand to include non-human primates and other vertebrate taxa to determine the canalization of this pattern. If this pattern is dictated by chondral modeling, it is possible it will differ among species with different locomotor regimes and thus different limb loading; alternatively, if this pattern is established more inflexible, robust developmental networks, we may find broader phylogenetic evidence for its persistence in vertebrates. Further, because a larger developmental network is less vulnerable to alteration during development and therefore results in less phenotypic variability (Sears, 2014), future work will also explore the developmental genetic underpinnings associated with joint morphology. If this rule applies to joint surfaces, presumably the concave articulations are formed by smaller, less integrated, less robust developmental networks which allows for more phenotypic noise to manifest in the adult morphology. By exploring the regulation and expression of genes associated with joint morphology, this hypothesis can be directly tested, a clearer picture of the differences in development and growth between the

convex and concave joint surfaces will emerge, and we can ultimately make headway in our understanding of joint morphogenesis.

From a macroscopic perspective, future studies will use the data collected here to analyze the local features of joint morphology that change in coordination with one another given their covariance relationships. Directly articulating morphologies with complementary function likely exhibit related changes in mirrored portions of their shapes given the functional need for semi-conformity between them. However, the expected shape coordination occurring between analogous structures exhibiting high covariance (e.g., distal humerus/distal femur) are less obvious and would require deeper investigation.

Local shape features of the distal femur were already investigated in Chapter IV of this dissertation, revealing specific shape traits to be characteristic of individuals with total knee arthroplasty. The analysis focused on the distal femur given the expectation that it was relatively invariant in relation to its concave surface of the tibial condyles, but future work will expand the analysis to include an investigation of the proximal tibia to determine whether coordinated variants are also occurring on the medial tibial condyle. It is possible that associated variation may be occurring in the tibial condyles given the increased propensity for these articular surfaces to vary relative to the femoral condyles; if significant variation related to TKA status could be detected even in the more morphologically restricted convex surface of the femoral condyles, it is likely that the more variable concave surface would exhibit variance, too. However, even if shape differences occur in the tibial condyles, it is also possible that it does not directly mirror the variation in the femur. If the differences in the medial femoral condyle are not met with corresponding tibial changes, this may decrease the congruence in the knee articulation; a decrease in congruence, even by as little as 0.3%, can alter contact distributions between

articulating surfaces and induce deleterious cartilage strain and subsequent onset of joint degeneration (Brandt et al., 1991; Kippel & Dieppe, 1994; Stone & Yu, 1997; von Eisenhart-Rothe et al., 1997).

Future work will also investigate whether individuals who needed knee replacements fall toward the extrema of the variance distributions presented in Chapter II, and if so, whether they fall toward the extrema for multiple joints, or only one. In other words, if an individual exhibits “extreme” morphology for one joint, what is the likelihood that they are extreme in other joints as well? With this information it may be possible to create risk assessments for each joint and identify, based on morphology, which joints are most predisposed to biomechanical degeneration.

Conclusion

Joint morphology is complex due to its role in locomotion and as the regions of interface between the long bones of the limbs. Articular shapes must correspond to neighboring morphology, achieve full ranges of motion that are consistent among most individuals, and maintain fit and stability throughout ontogeny and into adulthood. There is agreement that both biomechanical and chemical inputs are required to produce articular morphology, but that once definitive joint shapes are achieved, they do not experience cortical remodeling to the same degree as the long bone diaphyses.

The results of this dissertation establish previously unknown patterns of coordinated variation among the articular shapes of the shoulder, elbow, hip, and knee in contemporary humans. The most striking result is the differential variation between the convex and concave

surfaces across all joints under study (Horbaly et al., Chapter II). The consistency with which this pattern is observed across the human skeleton points to differential developmental processes between articulating surfaces belonging to the same joint, and both the broad morphological patterns and potential regulatory mechanisms behind them will be investigated in future research.

Another notable finding is that functional analogy—and in some cases, serial homology—between articular surfaces results in a covariance structure that overrides the association between directly interacting surfaces (Horbaly, Chapter III). All articulating morphologies that are complementary for function exhibit significant covariance, but the hierarchy of covariance strength runs counter to expectations of an inverse relationship between cartilage (meniscus, labrum) thickness and articular shape correspondence. Yet the highest covariance is observed between the analogous articulations of the proximal and distal humerus and femur. This again points to the strength of the underlying developmental mechanisms in patterning articular relationships in homologous limb segments.

Finally, the inextricable relationship between joint shape and movement evokes the possibility of a relationship between “abnormal” articular shape and joint degenerative diseases. Prior work has noted an apparent association between knee joint shape and osteoarthritis status, however, studies have not identified explicit features of articular morphology that may drive this relationship. The results of this dissertation corroborate those findings by demonstrating shape differences in the distal femora of skeletons who received a knee replacement during life and those who did not (Horbaly, Chapter IV), but further, I identify the medial femoral condyle as the main source of shape difference between the two groups. The medial curvature of the medial condyle occurs more anteriorly in individuals who received a knee replacement, and the posterior portion of the condyle exhibits a medial rotation. Though these differences may seem nuanced,

the clinical literature has demonstrated that even small alterations to joint morphology can have deleterious effects on biomechanics and wear patterns, and further, that the medial femoral condyle is among the most common points of degeneration in patients who need knee replacements.

Collectively, the findings of this dissertation evince a picture of how articular surfaces of the human limbs contribute to skeletal variance and covariance, and indicate how local shape variation may have clinical consequences.

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VITA

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