REVIEW ARTICLE

Entheseal Changes: Benefits, Limitations, and Applications in Bioarchaeology

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ABSTRACT

Reconstructing physical activities in ancient humans has long been pursued in bioarchaeology to understand our history and development. Entheseal changes (EC)—variations to muscle, tendon, and ligament attachment sites on bone—have been used in bioarchaeology since the 1980s to reconstruct activities in past populations such as changes in mobility, subsistence strategy, and gendered division of labour. EC research is based on bone functional adaptation, where bone responds to mechanical stress on entheses through bone formation or destruction in varying degrees of expression. However, the relationship between EC and activity is more complex than simple cause-and-effect, as it involves multiple confounding variables, which can affect EC morphology. This article addresses the use of EC research in bioarchaeology through two parts: Part 1 defines entheses and EC, including observational and quantitative methods developed in bioarchaeology to study EC. Part 2 will summarize the main known factors that influence EC beyond activity such as age, sex, and body size. The article concludes with a discussion of varying benefits and limitations to EC research in bioarchaeology including the use of archaeological samples, historical collections, and animal experimental models. Overall, EC research can be difficult to link with activity due to its multifactorial etiology, challenges of efficacy in developing methods, and limitations of working with human remains. However, recent studies are showing more positive results, demonstrating the usefulness of EC as a way to reconstruct activity.

Keywords: biomechanics, bone adaptation, bioarchaeology, entheseal changes, archaeology, activity reconstructions, methodology

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INTRODUCTION

Activity reconstruction from human remains has long been a significant focus in paleoanthropology and bioarchaeology as a way to understand past populations. Skeletal markers can be observed and quantified to reveal clues about physical activities within a population such as occupation, gendered divisions of labour, subsistence strategies, and mobility (e.g., Eshed et al. 2004; Hawkey and Merbs 1995; Lieverse et al. 2013; Yonemoto 2016). However, the relationship between activity during life and the skeletal markers they leave behind are consequences of a multitude of external and internal factors that complicate our interpretation (Jurmain et al. 2012). Currently, there are three widely used activity indicators in skeletal analysis that can provide context for these avenues of inquiry: cross-sectional bone geometry (CSBG), osteoarthritis (OA), and entheseal changes (EC).

This article uses EC as the primary indicator of activity for analysis. Given the current state of human EC research, this topic will be discussed based upon two main questions:

1. *How have EC been used in archaeological research as a method for reconstructing activity?*
2. *What factors influence EC etiology and what are the benefits and limitations of EC research?*

Each question will be addressed in two corresponding parts. Part one analyses the definition and current understanding of entheses and their two anatomical types, fibrous (FE) and fibrocartilaginous (FCE). This part describes EC and explains how they are understood in terms of bone biomechanics and includes a summary of the main EC literature and methods developed since the 1980s. The second part discusses the etiology of EC and how the effects of age, sex, body size, and other systemic factors influence entheseal morphology. Part two then examines the benefits and limitations of EC research and demonstrates how EC have been used to reconstruct past activity.

CONTEXT

The link between skeletal morphology and activity in bioarchaeology is based upon the widely accepted concept of bone functional adaptation (Ruff, Holt, and Trinkaus 2006). This concept may be best known through Wolff's Law as "form follows function", meaning that cortical and trabecular bone architecture will remodel and adapt to best disperse mechanical loading forces (Benjamin et al. 2006; Ruff, Holt, and Trinkaus 2006; Wolff 1986). Simply put, bone functional adaptation reflects the microdamage to bone and connective tissue caused by mechanical overloading, which stimulates the production of osteoblasts (bone-producing cells) and osteoclasts (bone-destructing cells) (Benjamin et al. 2006; Ruff, Holt, and Trinkaus 2006). This cell activity alters the architecture and morphological appearance of bone tissue as our skeletons continue through stages of growth, maintenance, and destruction over time (Benjamin et al. 2006; Ruff, Holt, and Trinkaus 2006). The variation and expression of these accumulated morphological changes can then be analysed in different ways to infer past physical activities, of which CSBG, OA and EC are the most popular indicators in bioarchaeology (Jurmain et al. 2012). Since these indicators are often used together to increase the accuracy of interpretations of skeletal morphology, it is important to briefly define their current role in bioarchaeological research.

CSBG analyzes changes to cortical bone structure and geometry on long bone diaphyses (bone shafts) in response to bending, twisting and compression from biomechanical loading (Becker 2020; Ruff, Holt and Trinkaus 2006). The shape and geometry of long bones can indicate general levels of activity in individuals or compare populations to reveal chronological changes in subsistence strategy such as hunter-gatherers to sedentary agriculturalists (Becker 2020). For example, the shape and volume of cortical bone on the lower limbs of a mobile forager would expect to be markedly different from a sedentary farmer when comparing bone cross sections due to the nature of bone adaptation to mechanical loading (Ruff, Holt, and Trinkaus 2006). However, researchers must also consider the impact of non-mechanical factors on CSBG such as hormones, diet, genetics, or age that can influence bone structure (Becker 2020; Jurmain et al. 2012).

OA is a chronic and degenerative condition of synovial joints characterized by a combination of inflammatory bone responses to hyaline cartilage breakdown (Lieverse et al. 2016; McGonagle, Hermann, and Tan 2015). Skeletally, OA can present as either marginal hypertrophic changes (osteophytes) or as pitting, porosity, or erosion on joint surfaces (Domett et al. 2017). It is ubiquitous in modern and ancient populations and is multifactorial in etiology, where physical activity, age, sex, genetics, and skeletal trauma experienced during life—such as fractures or infections—are all risk factors (Domett et al. 2017). Bioarchaeologists can use OA to describe general levels of physical activity in ancient populations when accompanied by archaeological evidence, strong statistical methods, and population-level comparisons (Becker 2020; Dommett et al. 2017; Jurmain et al. 2012).

Entheseal changes (EC) are the morphological alterations to *entheses*—muscle, tendon, and ligament attachment sites on bone—that occur as an adaptative response to biomechanical stress (Villotte et al. 2010). EC are also known in bioarchaeology as musculoskeletal stress markers (MSM) (Hawkey and Merbs 1995), markers of occupational stress (Kennedy 1983; İşcan and Kennedy 1989), evidence for occupation (Kelley and Angel 1987), activity-induced pathology (Merbs 1983), activity-induced stress markers (Hawkey and Street 1992) and, in clinical literature, as enthesophytes, enthesopathies, and enthesiopathies (Benjamin et al 2002, 2006; Jurmain et al. 2012). The recent shift of terminology to 'entheseal changes' was intended to avoid the assumption that occupation, activity, or pathological changes are the sole contributors to EC, which are now known to have a multifactorial etiology (Villotte et al. 2010).

PART 1: ETHNESEAL RESEARCH IN BIOARCHAEOLOGY

Entheses

As stated earlier, entheses are sites on bone to which muscles, tendons, and ligaments attach (Benjamin et al. 2002, 931). Each enthesis is different in size and shape, and their soft tissue attachments vary depending on their location on the skeleton (Benjamin et al. 2002, 2006). Tendons attach muscles to bone and facilitate movement, such as the Achilles tendon connecting the calf muscles to the calcaneus (heel), whereas ligaments connect bone to bone and provide joint stability, such as the anterior cruciate ligament (ACL) connecting the femur to the tibia and stabilizing the knee (Benjamin et al. 2002). When skeletal muscles contract to create movement, mechanical strain is transferred to the affected tendon or ligament. Here, mechanical stress is dissipated away from the hard-soft tissue boundary on the enthesis and distributed more evenly across the soft tissue structures, creating a stronger resistant force (Benjamin et al. 2002, 2006). The transfer of strain is essential for minimizing the risk of tearing and avulsion fractures in which the tendon or ligament is completely torn away from the enthesis because of mechanical overloading (Benjamin et al. 2002; Ruff, Holt, and Trinkaus 2006). Moreover, entheses tend to overlap with one another, and fasciae connect different muscles, which further solidify the bond between soft and hard tissue (Benjamin et al. 2006). Entheses are also part of an "organ complex," where anatomical structures surrounding the enthesis such as bursae and fat pads also assist in dissipating mechanical stress by reducing shock and friction on joints and are thus also affected by the same factors that influence entheseal morphology (Benjamin and McGonagle 2009).

Types of entheses: Fibrous (FE) and fibrocartilaginous (FCE)

Entheses are divided into two forms, fibrous entheses (FE) and fibrocartilaginous entheses (FCE) (Benjamin, Evans, and Copp 1986; Benjamin et al. 2002). FE develop through intramembranous ossification and are found closer to the diaphyses of long bones (Benjamin et al. 2002, 2006). FE have no cartilaginous tissue and are associated with large and powerful muscles in the body like the quadriceps and adductor muscles attaching to the *linea aspera* of the femur or the deltoid muscles of the shoulder (Benjamin et al. 2002). Thus, these entheses typically cover a larger surface area than FCE (Benjamin et al. 2002). FE are further subdivided into two types, periosteal and bony. The former denotes attachment indirectly onto bone via the periosteum––a layer of vascular connective tissue covering bone. The latter indicates direct attachment onto bone *without* involvement of the periosteum (Benjamin et al. 2002, 2006; Benjamin and McGonagle 2009).

Histologically, FE are bound by dense fibrous connective tissue and do not contain fibrocartilage, unlike FCE. In addition, extrinsic fibers (EF), previously named Sharpey's fibers due to their close anatomical similarity to those in the periodontal ligament of teeth, are a dense mat of collagen fibers that are responsible for anchoring tendons to the periosteum and directly onto the bone (Turcotte et al. 2020). EF are in the deepest aspects of the cortical layer where other fibers attach (Benjamin et al., 2002). These fibers are well known in some FE but not in FCE and are not found on entheses with little or no cortical bone (Benjamin et al. 2002). There is no definitive 'normal' or unchanged appearance of FE, but medical literature characterizes it by a smooth cortical surface (Villotte et al. 2016; Benjamin et al. 2002, 2006).

FCE are typically found on the epiphyses (ends of long bones) and closer to joint surfaces, attaching directly to the bone without any periosteal involvement. FCE also have four histological layers, from superficial to deep dense fibrous connective tissue (i.e., the tendon), uncalcified fibrocartilage, calcified fibrocartilage, and bone (Benjamin, Evans, and Copp 1986; Benjamin et al. 2002). The boundary between uncalcified and calcified fibrocartilage is called the tidemark, observed as the bony surface remaining after all soft tissue has been removed (Benjamin et al. 2002). On dry bone, a 'normal' or unchanged FCE presents as "smooth, well-circumscribed and devoid of vascular foramina" (Benjamin et al. 2002, 939) and has more visible boundaries than FE, which is why most new studies tend to focus on FCE only (Henderson et al. 2016, 2013; Villotte et al. 2016, 2010).

A new EC scoring method, dubbed the Coimbra method, also delineated FCE into two distinct zones (Henderson et al. 2013, 2016). Zone 1 is the small area on the outer portion of the enthesis that reflects the most oblique angle of tendon attachment, and Zone 2 is essentially the rest of the entheseal area (Henderson et al. 2016, 2013). Henderson's team argue that these zones are important to delineate because compressive and/or shear strain on a tendon—particularly at its most oblique angle—changes the molecular composition of bone's extracellular matrix. As such, Zone 1 normally forms a greater amount of fibrocartilage than Zone 2 as an adaptational response to mechanical loading, thus altering the appearance of attachment sites (Benjamin et al. 2006; Henderson et al. 2013, 2016).

Entheseal Changes (EC)

EC are non-pathological morphological changes that reflect bone formation or bone destruction through mechanical strain and other factors including age, sex, body size, and genetic variables (Henderson et al. 2016; Jurmain et al. 2012)). Bone *formation* is observed as osteophytic (bone-producing) cellular activity creating robusticity and rugosity (roughness) on cortical bone often characterized by bony crests, ridges, or enthesophytes (Foster, Buckley, and Tayles 2014; Hawkey and Merbs 1995). Bone *destruction* appears as various forms of osteolytic (bone-reducing) erosions, cavitations, macroporosities, and microporosities in bone (Henderson et al. 2013, 2016).

In terms of bone functional adaptation, the main idea in EC research is that increased muscle use through physical activities increases strain on human tendons or ligaments and causes microscopic damage and tears to connective tissue. This damage increases blood flow to the attachment site, in turn, encouraging bone cell activity that alters the shape, size, and appearance of the enthesis (Jurmain et al. 2012).

Based on this understanding, entheses that show more morphological changes are attributed to greater amounts of physical activity. This allows researchers to discern patterns of activity in archaeological contexts (Jurmain et al. 2012). The frequency, duration, and extent of loading also contribute to the varying expressions of EC in addition to the type and anatomical location of the enthesis on the skeleton (Ruff, Holt, and Trinkaus 2006). It should also be noted that the appearance of a "normal" FE and FCE¬—that is, the absence of EC—does not imply that the individual did not participate in activities, as EC etiology is multifactorial. Thus, the absence or presence of morphological changes and their overall degrees of expression do not necessarily reflect the intensity or duration of activity during life (Dewey 2018).

Pathological changes to entheses are often caused by overuse injuries. Overuse injuries can be anything from "jumpers' knee" on the patella to "tennis elbow" in the humeral epicondyle in athletes, or can reflect inflammatory, metabolic, traumatic, or degenerative conditions such as spondyloarthropathies, OA, and diffuse idiopathic skeletal hyperostosis (DISH) (Dewey 2018; Jurmain et al. 2012). These changes, called *enthesopathies* in clinical literature, are an abnormal osteolytic or osteophytic response to the above conditions, and are not considered EC in its most recent definition (Jurmain & Villotte, 2010; Villotte & Knüsel, 2013). However, multiple scoring methods (see Hawkey and Merbs 1995; Mariotti, Facchini, and Belcastro 2004; Villotte et al. 2010) incorporate enthesopathies and other pathological lesions into their scoring methods through aggregate scores that consider normal and pathological changes either together or separately. The incorporation of pathological changes on entheses are still important to consider as they are intrinsic to the enthesis organ and thus affected by the same biomechanical forces. However, the exclusion of pathological changes in recent terminology was intended to avoid implicit associations between EC and pathological origins (Jurmain and Villotte 2010; Villotte and Knüsel 2013).

Methods for EC Analysis: Observational Scoring Systems

Research on EC in the 1980s and 1990s introduced various nonmetric and visual scoring methods of entheses using skeletal remains from archaeological sites (e.g., studying effects of occupational stress in Kelley and Angel 1987). Diane Hawkey and Charles Merbs (1995) were the first scholars to introduce the first well-known standardized scoring method in bioarchaeology intended for repeated use. This method considered three EC features each scored on a three-point ordinal scale on FE and FCE alike: stress lesions, ossification exostoses (enthesopathies), and robusticity markers (Hawkey and Merbs 1995). This method was the first to use a ranked scoring structure and standardize morphological expressions, which allowed other researchers to comparatively identify common links between EC expression and activity. However, many scholars have criticized this method for failing to incorporate clinical entheseal research, being overly simplistic, and having poor intraobserver and interobserver repeatability (e.g., Davis et al. 2013). Some authors recommend modifying this method in future studies by combining all three features' scores (on a scale of zero to six) to indicate total muscle use, allowing the results to be less sensitive to anomalies, instead focusing on broad activity levels rather than individual muscle use (Molnar 2006; Weiss 2007).

Another popular nonmetric methodology similar to Hawkey and Merbs (1995), created by Valentina Mariotti, Fiorenzo Facchini, and Maria Giovanna Belcastro (2004; 2007), also applies to both FE and FCE. This method analyzes robusticity and two different categories of enthesopathies: osteolytic lesions and osteophytic lesions. In addition, reference photographs of each score from one (minimal expression) to three (strongest expression) on each recorded enthesis are provided (Mariotti, Facchini, and Belcastro 2004, 2007). Notably, this scoring method was tested using a historically identified skeletal collection of 19th and 20th century Europeans, whereas Hawkey and Merbs (1995) applied their scoring method to archeological Inuit remains[1]. 'Historically identified' refers to individuals or populations (in this case, curated skeletal collections) that have accompanying documentation of their age-at-death, date of birth, sex, occupation, and any other information detailing their life histories useful for testing EC methods. However, the use of historically identified skeletal collections does not render this method infallible, since Mariotti and colleagues' work has also been criticized for failing to include clinical entheseal research and for their high intraobserver and interobserver variability for scoring robusticity (Jurmain et al. 2012; Villotte and Knüsel 2013). Additionally, these collections are useful in that they provide more accurate data on age and sex than in archaeological remains. However, future scholars must consider and consult the modern descendants of these remains when necessary, particularly when contributing to ethical Indigenous research and reciprocal Indigenous-non-Indigenous relationships over exploitative, colonial interpretations of Indigenous remains.

Sébastien Villotte and colleagues (2007, 2010) developed a visual scoring method that incorporated medical literature on entheses. The focus of the scoring method was the distinct anatomy and histology of FE versus FCE. As stated previously, FCE and FE are different in their histology and location, reflecting different molecular responses to biomechanical strain and thus their manifestation of EC. For example, fibrocartilaginous tissue is present only on FCE and increases as an adaptation to compression and/or shearing forces in the deeper part of an enthesis (i.e., closer towards the center of the attachment) compared to its more superficial parts, thus resulting in different entheseal morphology (Benjamin et al. 2002; 2006). Indeed, their tests on a historically identified collection showed a positive correlation between activity and changes to FCE. However, they found no link between activity and FE, thus reinforcing the suggestion that FE and FCE show EC differently and should be scored separately (Villotte et al. 2010).

A newer standardized method in EC research, dubbed the Coimbra method (Henderson et al. 2013, 2016), was developed exclusively for FCE. Two previous scoring methods developed by Mariotti, Facchini, and Belcastro (2004, 2007) and by Villotte and colleagues (2010) served as the basis for this new protocol. The method considers six categories of entheseal morphological variation: textural change, bone formation, erosion, fine porosity, macroporosity, and cavitations. Further, this method also divides the enthesis into two zones, Zone 1and Zone 2, where Zone 1 is the thin margin along the border of an enthesis that represents the most oblique angle of attachment for the tendon or ligament, and Zone 2 is the rest of the entheseal surface (Henderson et al. 2013, 2016). This method incorporates medical literature and considers the effects of age, sex, and body size in their scoring methods, which has allowed for higher observer repeatability and shows potential as a reliable method for future EC research (Henderson et al. 2013, 2016).

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[1] According to Hawkey and Merbs, the Inuit remains used in this study were recovered between 1967 and 1969 during the "Northwest Hudson Bay Thule Project" (1995). Their justification for utilizing these skeletal remains was their good preservation and "cultural and genetic isolation", which allowed the authors to connect their results to specialized activities associated with this population. However, this article fails to include any mention of ethical concerns or consultation with Indigenous communities leaving many questions surrounding the effects of research based on bone collections held in colonial institutions, like museums and archives, on modern Indigenous peoples as well as reconciliation and repatriation efforts.

Methods for EC Analysis: Quantifying Entheseal Dimensions Using 3D Surface Models and 2D Topography

Although nonmetric scoring systems based on visual analysis served as the basis for most early research on EC, there are some drawbacks to these methods. The first limitation is the influence of human subjectivity affecting observer bias, and the second is the low statistical power of ranked scoring systems (typically zero to three), which reduces observer error but also negatively impacts the detection of statistical patterns linking EC and activity (Havelková and Villotte 2007; Nolte and Wilczak 2013). Given the increased availability and lowered costs of computers and laser scanning technology at the turn of the twenty-first century, EC methodologies that use quantitative computational data like two-dimensional (2D) topographical analysis and three-dimensional (3D) models of entheses, have become more popular. These methods are beneficial in that they have high repeatability and precision compared to observational scores and counter the drawbacks of low statistical power in nonmetric systems, opening new avenues of precise data analysis for EC research. Quantitative analysis has also proven useful in experimental studies that use animal models as human proxies (Rabey et al. 2015; Wallace et al. 2017; Zumwalt 2006), where 3D laser scanning and topographical analysis of entheseal structures are employed to identify any links between EC and activity.

The first application of digital technology for EC utilized entheseal measurements to study their linear profiles via 2D topographical analysis and optometric scanners to quantify the size and surface roughness of FE and FCE on human remains (Pany-Kucera, Viola, and Teschler-Nicola 2009; Wilczak 1998). Monica Nolte and Cynthia Wilczak's subsequent study in 2013 investigated the effects of biological variables (age, sex, body size, and secular changes) and quantified FCE of the upper limb using Next Engine 3D scans on skeletal collections. Efthymia Nikita and colleagues (2019) introduced another approach that considered the shape of the *supraspinatus*, *infraspinatus*, and *subscapularis* entheses on the humerus (muscles that attach on the shoulder blade and connect to the upper arm) by adopting a 3D microscopic method. Though these works failed to find strong links between EC and activity, they draw attention to the importance of considering impacts of biological variables (e.g., age, sex, and body size) and how different quantification methods can be beneficial to EC research (Nikita et al. 2019; Nolte and Wilczak 2013).

Other researchers have considered the relative size of entheses to identify EC and activity patterns including the series of publications by Karakostis and colleagues, particularly Karakostis and Lorenzo (2016). This research by Karakostis and colleagues explore the development of hand entheses by introducing a 3D recording method for entheseal area (Karakostis et al. 2017). When testing this method, they quantified entheseal surface area in a skeletal collection and identified patterns in individuals of similar activity levels (e.g., individuals with high manual labor occupations versus low manual labor) (Karakostis et al. 2017). After criticisms of low interobserver and intraobserver repeatability in this method, Karakostis and colleagues (2018) introduced a new method analyzing the *shape* of entheses using 3D landmark-based geometric morphometrics and multivariate statistics. Recent publications in EC research encourage the use of multivariate analysis to control for confounding variables affecting EC etiology (e.g., Millela et al. 2015). Statistical protocols that consider multiple contributing variables in EC morphology allow researchers to better identify links between EC and activity, countering the obscuring effects of age, sex, and body size on EC scores to an extent (Milella et al. 2015).

Considering this, Fotios Alexandros Karakostis and colleagues (2018) developed a new 3D approach found to be highly repeatable and addressed the limitations of previous studies using topographical analysis because previous methods could not measure the variation in the shape of multiple landmarks on an enthesis simultaneously. Morphometric geometric analysis thus seems effective when applied to historical skeletal collections and archaeological remains (Karakostis et al. 2018). Karakostis and colleagues (2021) subsequently published a case study identifying a specific pattern of EC on the hand in an approximately 8,500 cal. BP individual from the Peruvian Andes. EC on the thumb and fingers were associated with precision gripping, suggesting that this method is sensitive enough to identify precise muscle activities in past individuals and shows potential for future EC research (Karakostis et al. 2021).

PART 2: EC ETIOLOGY, BENEFITS, AND LIMITATIONS

EC and Age

It was noted in early EC research that entheses typically showed more pronounced morphological changes in older individuals, and this trend has proven consistent in more recent studies testing EC scoring methods on skeletal collections (Henderson et al. 2016; Mariotti, Facchini, and Belcastro 2004; Milella et al. 2012; Molnar 2006; Niinimäki 2011; Villotte et al. 2010). The high correlation between increased age and pronounced morphological expression is also relatively consistent in studies testing the efficacy of multiple different visual scoring methods on the same skeletal collection. For example, a study by Efrossyni Michopoulou, Efthymia Nikita, and Efstratios Valakos (2015) used the Athens Collection to test methods developed by Hawkey and Merbs (1995), Mariotti, Facchini, and Belcastro (2004), and Villotte and colleagues (2010). A subsequent test of the Coimbra method using the same testing parameters found age to be a less significant causative factor when compared to previous scoring methods (Michopoulou, Nikita, and Henderson 2017). The authors attributed their results to the method's greater efficacy rather than suggesting that age was a lesser causative factor.

These observations suggest that age obscures distinctions between EC and activity. For example, Niinimäki (2011) found that score differences between populations of heavy and light manual labourers were consistently higher in heavy manual labourers, but scores were equal between labour groups after the age of 50. This raises many questions between the connections between age, EC, and activity such as does this mean that these individuals transitioned to lighter manual work as their bodies aged? Or does it mean that the effects of age-associated degeneration obscure the impacts of physical activity? Michopoulou, Nikita, and Henderson (2017) attributed this to the 'leveling off' process, whereby EC increase with age until around 40 to 50 years when physical activity typically decreases, and their bodies are biologically limited to respond to mechanical stress.

The observed prominence of age as a confounding variable of EC may be due to a few factors: the reduction of osteoblastic activity as a by-product of aging, the resorption of bone because of muscle underuse, and/or the accumulation of stress on bone in old age from years of wear and tear, overuse, and isolated events of physical trauma (Henderson et al. 2016; Michopoulou, Nikita, and Valakos 2015; Michopoulou, Nikita, and Henderson 2017; Niinimäki 2011; Villotte and Knüsel 2014). In addition, the relative association between EC and age seems to vary among different populations, suggesting that age effects on EC may be related to physical activity in and of itself (Yonemoto 2016). Charlotte Henderson and colleagues (2016) point out that age effects on the skeleton have numerous components that are still poorly understood. Given the multifactorial impacts of age on the human musculoskeletal system, for instance, it is difficult to determine these factors without additional multivariate analysis to control for other confounding variables such as body size, sex, and other historical data (e.g., indicating occupation, environment, population genetics, and any other influential factors). Nonetheless, research shows that age seems to have a statistically significant impact on EC morphological expression (Henderson et al. 2016; Mariotti, Facchini, and Belcastro 2004; Milella et al. 2012; Molnar 2006; Niinimäki 2011; Villotte et al. 2010; Weiss 2003, 2004, 2007).

EC and Body Size

In addition to age, body size has been noted as a statistically significant contributor to EC morphological variation (Foster, Buckley, and Tayles 2014; Weiss 2003, 2004, 2007; Wilczak 1998; Zumwalt 2006). Considering bone functional adaptation and gravitational effects on muscle size, larger bodies require larger muscles to meet the basic demands of movement and stability, which by extension affects their morphological expression on entheses (Foster, Buckley, and Tayles 2014; Ruff, Holt, and Trinkaus 2006; Villotte et al. 2010; Weiss, Corona, and Schultz 2012). This relationship has been identified in studies using skeletal measurements as proxies for body size (Niinimäki 2011; Weiss 2003; 2015) and studies testing entheseal surface areas where body size was found to be the most significant variable correlating with entheseal area (Nikita 2019; Nolte and Wilczak 2013;). Further, body size has been found to affect lower limbs more than upper limbs, being attributed to higher load-bearing requirements of the legs in enabling bipedal locomotion and body support (Ruff, Holt, and Trinkaus 2006; Weiss 2003, 2015; Weiss, Corona, and Schultz 2012). Body size also affects entheseal types differently, as studies show that FE correlate with body size more than FCE because FE attach to larger muscles and over a broader area of diaphyseal bone (Villotte et al. 2010; Weiss 2015).

Interestingly, using skeletal measurements to calculate body *mass* rather than body *size* (the difference being the use of different skeletal measurements and calculations, see Ruff et al. 2012) has also shown different correlations to EC. Michopoulou and colleagues (2015, 2017) noted that body size had a less significant correlation to EC scores in their study when using upper limb measurements to determine body mass. This contradicts earlier findings that used skeletal measurements to determine body size (e.g., Weiss 2003; 2004; 2007; 2015; Niinimäki 2011; Weiss, Corona, and Schultz. 2012). However, Michopoulou, Nikita, and Henderson state that

> "…it must be stressed that earlier studies had used specific bone dimensions as a proxy for body size, rather than body mass…[i]t is possible that although body mass is a better overall measure of body size, the dimensions of the bone elements on which the ECs have been recorded approximate body size more directly concerning the ECs under study" (2017, 415).

This implies that measurements for body mass as a proxy for body size is a more accurate indicator, and that stronger correlations between body size and EC expression found in earlier studies may be partially explained by the researcher's choice of bone dimensions as proxies for body size. Therefore, the impact of body size and the measurements used to calculate body size versus body mass show different correlations to EC, which requires further study.

In general, body size has a stronger correlation with lower limb than upper limb EC and affect FE more than FCE, probably due to their anatomical differences in muscle demands in resisting gravitational and biomechanical forces (Foster, Buckley, and Tayles 2014). However, the measurements used to calculate body mass as proxies for body size show differing correlations to EC scores than previous findings; thus more research is required to fully understand the impact of body size on EC (Michopoulou, Nikita, and Valakos 2015; Michopoulou, Nikita, and Henderson 2017). In addition, the entanglement of body size as an innate characteristic of sexual dimorphism complicates the distinction between these two factors, as will be described further.

EC and Sex

Most EC studies have found that males typically show greater EC expression than females. This observation has prompted scholars to suggest that these sex differences are largely a result of sexual dimorphism in body size (Niinimäki 2011; Weiss 2003, 2004, 2007, 2015; Weiss, Corona, and Schultz. 2012). However, Weiss (2015) points out that the correlation with size disappears when controlling for sex or considering male and female scores differently in both the upper and lower limbs, implying that hormonal sex differences may be more responsible for these observations than body size (Weiss 2004, 2007, 2015; Weiss, Corona, and Schultz 2012). Indeed, males should be expected to have larger entheses than females since males have higher ratios of muscle mass to body size due to testosterone levels experienced during and after adolescence (Foster, Buckley, and Tayles 2014). Thus, although muscle size correlates with entheseal size, this relationship should not imply causation and may not fully account for innate traits of sexual dimorphism. Additionally, the different measurements of body size versus body mass as proxies must be considered to avoid introducing further error.

In early publications, differing EC scores by sex were attributed to males engaging in higher activity levels than females due to gendered division of labor rather than innate sexual differences (e.g. al-Oumaoui, Jiménez-Brobeil, and du Souich 2004; Hawkey and Merbs 1995). Likewise, cases with reverse sex differences—females showing higher EC scores than males—were also assumed to result from higher activity levels in gendered tasks. For example, Eshed and colleagues (2004) attributed high EC scores in the upper limb of Natufian females to gathering and grinding activities, and Hawkey and Merbs (1995) attributed higher *trapezius* scores in female Inuit to their role in *umiak* rowing. These interpretations have been criticized for their oversimplification of EC scores being attributed to gender-structured activities instead of biological sex. However, more contemporary studies confirm that sex differences in EC scores can be partially attributed to these social factors, particularly in the upper limb, where the impact of body size is reduced (Mazza 2019; Weiss 2015).

Overall, authors still disagree as to whether sex or body size is the most influential factor for EC. Given the interconnected nature of body size with innate hormonal characteristics of sexual dimorphism, some authors argue that body size need not be controlled for at all, citing the connection between sexual dimorphism and body size (Villotte et al. 2010; Weiss 2003). However, sex impacts the expression of EC, particularly in the upper limb(s), where body size has less influence, indicating that body size and sex should not be considered equal in their influence on EC morphology (Weiss, Corona, and Schultz. 2012; Weiss, 2015).

EC and Other Genetic Factors

Although age, sex, body size, and activity are the primary influencers of EC expression, other genetic factors can explain some of the observed variation in EC morphology (Jurmain et al., 2012). Considering muscle tissue, Foster, Buckley, and Tayles (2014) note that the amount of muscle fiber determines a muscle’s mass and shape, and by extension, impacts the morphology of an enthesis. They explain that muscle size increase via physical activity causes hypertrophy in muscle fibers rather than increasing fiber numbers themselves. Instead, muscle fiber number is genetically determined, implying "a genetically imposed limitation to muscular development based on the numbers of fibers available to respond to stress" (Foster, Buckley, and Tayles 2014, 524). In addition, genetic variation also influences average muscle size in males and females, suggesting that population genetics has an impact on the expression of EC through its influence on muscle morphology (Foster, Buckley, and Tayles 2014). Moreover, Benjamin and colleagues (2006) note a genetic influence on the presence of enthesophytes on the skeleton, where some individuals are "bone formers" and more prone to osteogenesis in reaction to mechanical stress than others (Rogers et al. 1997). This suggests that some populations may show higher EC scores than others despite similar levels of activity. These examples do not encompass all possible impacts of genetics on EC, but serve as a reminder that the multifactorial etiology of EC depends on many variables other than age, sex, and body size, and that these should also be considered.

Other Benefits and Limitations of EC Research

As stated earlier, EC have been used to study archaeological human remains to provide valuable information about past activities and behaviours of ancient peoples. This can include social relationships such as division of labour among age, gender, and other social categories, and changes in occupation, mobility, and/or physical activity over the life course. Yonemoto (2016), for instance, compared the EC of Japanese males from four historical sites known for different occupations from the fifteenth, seventeenth and nineteenth centuries: fisherman, salt producers, samurai, and townspeople, respectively. She found that significant EC differences were found between individuals of different classes and occupations, and each population showed variations among age categories as well, particularly between young adults (aged 20 to 40 years) and old adults (aged 60 plus years) (Yonemoto 2016).

EC in the lower limbs among the samurai group shows little change across age categories. This was attributed to the formalized and consistent behaviours of samurai etiquette throughout their lives. In contrast, the wide variability of EC among the townspeople reflects their different occupations that required various levels of physical labor (Yonemoto 2016). Differing EC in the fishermen's knee and ankle joints according to age category reflects historical documentation describing how younger men would be responsible for tasks with high manual labor (such as loading and unloading nets onto boats), while older men would take less physically intensive roles such as sea navigation. Similarly, younger age categories of salt producers showed slightly lower levels of EC than older adults, though the *profile* of EC remained similar. This suggests specific entheses exhibiting greater changes were consistent between age classes, signifying differing age roles of the same occupation (Yonemoto 2016).

In another example, Lieverse and colleagues (2013) examined lower limb EC of three spatiotemporal populations of foragers occupying the Cis-Baikal region of Siberia over approximately 4,000 years. Their study found that the femora of one population—the Kitoi mortuary complex dated approximately 8,000 to 6,000 years ago—showed higher femoral loading and knee degeneration in males than other populations (Lieverse et al. 2013). This indicates increased mobility across steep and uneven terrains while bearing heavy loads (Lieverse et al. 2007, 2011; Macintosh 2011). These communities were large, likely resulting in rapid resource depletion and the need to travel more extensively (Weber and Bettinger 2010; Lieverse et al. 2013). In contrast, the Isakovo, Serovo, and Glazkovo mortuary complexes from the Late Neolithic-Early Bronze Age showed lower EC scores (Lieverse et al. 2013). These groups had lower population density and higher spatial distribution than the Kitoi, meaning they did not require extensive travel to acquire resources (Lieverse et al. 2013; Losey, Nomokonova, and Goriunova 2008). This interpretation is also supported by OA and CBSG studies in the same region (Lieverse et al. 2016; Lieverse 2010; Lieverse et al. 2011; Stock et al. 2010). Therefore, when accompanied by supporting environmental and historical data, archaeologists can infer physical activities of past populations.

Although these studies demonstrate the usefulness of EC in reconstructing activity in past populations, there is a limitation to using EC methods on archaeological remains, which may impact interpretive accuracy: archaeological human remains are not typically accompanied by extensive documentation listing the occupation, sex, and age-at-death of each individual. For studies wishing to test the efficacy of EC methodologies and their ability to identify links between EC and activity, authors refer to the use of historically identified skeletal collections.

Testing scoring methods on skeletal collections with documented life histories is beneficial for EC research for several reasons. First, it allows the comparison of scores between categories of occupations with low and high levels of physical activity (i.e., a tailor or clerk compared to a stonemason or builder), as well as other factors influencing EC such as age, sex, and body size that can help identify links between EC and activity (Alves Cardoso and Henderson 2013). An EC scoring method can also be tested on multiple collections, and multiple scoring methods can be tested on a single collection, allowing identification and refinement of observer error as well as comparisons of the efficacy of scoring methods (Michopoulou, Nikita, and Henderson 2017; Michopoulou, Nikita, and Valakos 2015). Second, historical collections are typically larger ($n \geq 100$) than archaeological samples (Henderson and Nikita 2015). Charlotte Henderson (2013) published a meta-analysis showing the median number of individuals used in previous archaeological studies for EC research to be around 15 to 44 individuals. Having larger sample sizes is important because it considers a larger variety of morphological variability and reduces bias of limited demographic profiles (Henderson and Nikita 2015). Finally, using historical collections in EC research reduces the effects of confounding variables such as age, sex, and body size, which can be controlled to a greater degree of accuracy than with archaeological remains.

A notable limitation to using identified skeletal collections is that they cannot accurately reflect similar EC patterns of past populations based on chronological differences in activity levels and social or economic structure. For example, EC from a documented collection of skeletons from a 19th-century agricultural population would not accurately compare to the EC of ancient hunter-gatherer populations in terms of physical activity and mobility. Since EC are multifactorial, differences in age, sex, and body size between populations would undoubtedly affect EC morphology differently, as would other factors such as diet and population genetics (Alves Cardoso and Henderson 2013; Foster, Buckley, and Tayles 2014).

Another limitation is that the reliability of historic demographic information varies from collection. Some skeletal collections lack documentation on age and sex, so these variables must be estimated using skeletal measurements of individual specimens (Alves Cardoso and Henderson 2013; Henderson and Nikita 2016). Even in collections with well-documented life histories, historical data are not infallible and must be regarded with caution. In particular, the documentation of activities is highly variable. Many collections are largely focused on males and only list known occupations at the time of the individual's death, failing to specify other physical activities, clinical histories, socioeconomic status, or hobbies during their life histories which have an unknown effect on the morphology of EC (Alves Cardoso and Henderson 2013).

Francisca Alves Cardoso and Henderson (2013) demonstrated this limitation by analyzing two Portuguese skeletal collections, 211 male skeletons from the Coimbra collection and 107 male skeletons from the Lisbon Luis Lopes collection. They applied three different methods of categorizing occupation as used in previous scoring methods developed by João Roque (1988), Alves Cardoso and Henderson (2010), and Sébastien Villotte and colleagues (2010). These categories split occupation by ranked levels of presumed physical activity (such as non-manual, light manual, and heavy manual), or type of occupation (for instance, 'government and services,' 'unskilled workers,' 'skilled workers/artisans,' 'farmers/servants', and 'commerce/transport) and found that EC scores varied considerably. Occupations like stonemason, weaver, and photographer were grouped in the same category using Roque's (1988, cited in Alves Cardoso and Henderson 2013) method (skilled workers/artisans), but when using the method by Villotte and colleagues (2010), stonemasons would move to manual or heavy manual, weavers to light manual or manual, and photographers to non-manual (Alves Cardoso and Henderson 2013, 194). In terms of finding statistical links between these activity categories and EC, the sole significant factor in almost all cases was age (Alves Cardoso and Henderson 2013). In addition, occupational categories were considered differently depending on the language of origin. In Portuguese, the word *lavrador/agricultor* (farmer), for example, could refer to tenant farmers, landless day laborers, dependant poor, or wealthy landowners. As for disparities of sex, the authors point out that female skeletal remains have far less comprehensive documentation in the Coimbra collection, where many occupations were listed as *domésticas* (housewife/housekeeper). This research draws into question the inherent subjectivity of classifying occupation and the interpretations of previous studies using EC methods on historical collections (Alves Cardoso and Henderson 2013).

Using Experimental Animal Models

A major limitation to EC research is our lack of insight into the direct relationship between muscle use and entheseal morphology. This problem can be addressed through experimental studies where the duration, intensity, and repetition of muscle use can be controlled and its effect on entheseal structure can be assessed. To date, three experimental studies using animal models have been performed to test the relationship between EC and activity, of which the first was performed by Ann Zumwalt (2006). Her model exercised ten sheep on treadmills (60 min/day for 15 min intervals) for 900 total hours while wearing weighted packs. Six 3D laser scanned entheses on the forelimb and hindlimbs showed that, although muscle size significantly increased as a result of activity, there was no difference in entheseal hypertrophy or surface complexity for either group. She concluded that her experiment could not find a link between EC and activity, citing instead the impact of body size on EC morphology (Zumwalt 2006).

Another study by Karyn Rabey and colleagues (2015) used a juvenile mouse model to perform different physical activities such as climbing and wheel running and assessed changes to bone growth, muscle fiber architecture, and entheseal morphology on the humerus. The climbing and running groups were observed over 78 days, with climbers traveling an average distance of 140 meters per night and the wheel runners ran around 1900 meters per night (Rabey et al., 2015). Comparing these factors among the sedentary, climbing, and wheel-running groups after digital processing, mice in the climbing group had larger muscle mass and shorter fiber length than the other two groups (Rabey et al., 2015). The wheel runners had the smallest muscle mass and the longest fiber length. In addition, cross-sections of diaphyseal bone revealed cortical bone growth in both exercise groups (after fusion of the humeral growth plate) was larger than the sedentary group (Rabey et al., 2015). However, like Zumwalt's (2006) results, Rabey and colleagues (2015) failed to find any difference in entheseal morphology across all three groups despite the changes to muscle mass, fiber length, and cortical bone structure, concluding that there was no observed link between EC and activity.

The third experimental study performed by Ian Wallace and colleagues (2017) examined the lateral epicondyles on the femora of ten female Eastern wild turkeys. The experimental group ran on a declined treadmill for 30 min per day, four days a week, for ten weeks. After laser scanning the femora and producing 3D models, the dimensions of the entheseal surface was quantified using topographical analysis (Wallace et al. 2017). Although changes in limb bone structure were apparent¬¬—exercised turkeys had a 21% increase in trabecular volume—there were no observed changes to entheseal morphology. The authors also concluded that their experiment found no link between EC and activity (Wallace et al. 2017).

The results of these experiments may seem disappointing, but there are some limitations to these studies that may explain this lack of connection compared to studies using observational data on human remains. First, the use of animal models as proxies cannot directly predict or reflect the same response to biomechanical stress in humans because bone functional adaptation is different in every species (Ruff, Holt, and Trinkaus 2006). Second, the experimental parameters are limited in their ability to test the type, duration, and intensity of physical activity required to cause EC, and, thus, cannot accurately reflect the activities of past human populations. It is doubtful that the average hunter-gatherer or agricultural community limited their exercise to less than an hour per day, and the moderate activity level the animal models were subjected to do not accurately reflect the high physical requirements of surviving in past living conditions. Finally, the methods of data analysis in these studies may be inappropriate for observing changes to entheseal morphology. Some digital technology used for 3D scanning and topographic analysis are considered outdated or may have been improved since the times of publication, introducing the possibility that outdated methods were too imprecise to detect microscopic changes to entheses (Karakostis et al. 2018).

Despite the lack of observed links with entheseal morphology to activity in these studies, valuable information can be gained from the observed changes to soft muscle tissue and bone in these experiments. Analyzing the differences in muscle fiber length and volume between climbing and wheel-running mice offers insight into what types of activity (endurance versus strength training) cause changes to these tissues (Rabey et al. 2015). These experiments also encourage potential longer-term studies that more accurately model the types of activities characterizing past human populations. For example, a study by Karakostis and colleagues (2019) look at the same turkey femora from the experiment performed by Wallace and colleagues (2017) and re-analyzed the femoral lateral epicondyles using a novel quantification approach of 3D principal component analysis (PCA) and multivariate statistical analysis. Surprisingly, this analysis method *was* able to detect different entheseal morphological patterns between control and experimental groups, demonstrating that future analytical techniques may be employed to identify links between EC and activity in studies that previously failed to document these associations (Karakostis et al. 2019).

CONCLUSION

Since the 1980s, EC have been used in bioarchaeology to describe the physical activity and mechanical stress in past populations, though this direct relationship remains unclear. Entheses are now understood to present in two distinct types, where FCE are better understood in terms of morphology and etiology than are FE. Entheses, in general, vary in size, shape, and density depending on their location in the body. Though the manifestation of enthesopathies have been included in most early visual scoring methods, contemporary EC research normally does not include these pathological lesions. In addition, EC are multifactorial and highly dependent on an individual's age at death, body size, sex, and other genetic factors. These confounding variables may affect EC morphology more than do activity, occupation, and mechanical stress.

Despite this, archaeological studies using EC have shown some convincing relationships between muscle attachments and activity when accompanied by contextual data. However, archaeological sites normally have small sample sizes, which is not the best for testing the efficacy of EC. Instead, methods are tested on historically identified skeletal collections, but there are inherent biases in the composition of these collections and limitations regarding collection documentation and occupational terminology.

Experimental studies using animal models such as sheep, mice, and turkeys to test the relationship between EC and activity have revealed valuable insights into the changes of muscle and tendon tissues, despite the lack of connection to entheseal morphology. Encouragingly, a recent 3D approach using PCA and other multivariate statistics has identified morphological changes to entheses in one animal study where the analytical methods in the original publication did not, demonstrating potential for future research on experimental studies using animal models. Overall, as EC research continues to incorporate clinical literature, refine visual and quantification methods, and employ appropriate statistical analysis on skeletal remains in humans, this field will undoubtedly reveal more avenues of application for EC as a way to reconstruct activity.

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