Sex Differences in Human Tibia Cortical Bone Morphometrics from Computed Tomography (CT)

Randee L. Hunter, Karen Briley, Amanda M. Agnew

Abstract Tibia fractures account for the majority of lower extremity injuries during pedestrian-vehicle interactions. Skeletal development, adaptation and degradation vary throughout the lifespan of males compared to females, underpinning sex-specific responses to loading. The purpose of this study is to quantify sex differences in tibia cortical bone morphometrics as they relate to age and body size. Quantitative computed tomography (QCT) analyses were performed on 128 cadaveric ex vivo tibia. Total area (Tt.Ar), cortical area (Ct.Ar), cortical thickness (Ct.Th), robustness (Tt.Ar/Le), area moment of inertia (I), and volumetric bone mineral density (vBMD) were quantified. Males had significantly larger morphometrics throughout the tibia ($p<0.005$), with the exception of vBMD ($p>0.17$). Sex-specific linear regressions demonstrated varying patterns between males and female with age. Female tibiae were more sensitive to mass as all morphometrics increased significantly ($p<0.01$) with body mass, with the exception of Ct.Th and vBMD. Body size was unable to predict male morphometrics, with the exception of proximal Ct.Ar and vBMD. Differential patterns in tibia parameters and sex-specific effects of age and body size suggest these should be accounted for in injury risk predictions rather than simply scaling male data to represent females.

Keywords Cross-sectional geometry, Injury risk, Lower extremity, Sex, Bone morphometrics.

I. INTRODUCTION

Injury and fatality following pedestrian-vehicle impacts remain a global issue. In the USA, over 129,000 pedestrians were treated in emergency departments in 2015 [1]. In 2017, there were 5,971 pedestrian fatalities, an increase of 1.7% from 2016, of which 70% were males and 30% were females [2]. Although rarely fatal and with only a maximum AIS3 severity, lower extremity injuries are the most commonly affected region of the body during these impacts [3], but recovery is costly and time-intensive [4]. Tibia fractures account for the majority of these injuries and commonly result from lateral blunt force impacts with the bumper of the vehicle [3][5-6]. Previous studies have explored the injury tolerance of the tibia [7-8] to create injury risk functions. Following Mather's [9] conclusions that smaller dimensions rather than sexual dimorphism in material properties drive the differential response of the tibia in females compared to males, scaling techniques assuming similar but size-dependent geometric properties were created [10]. However, skeletal development, adaptation, and degradation vary throughout the lifespan of males compared to females, underpinning sex-specific geometry of long bones driving differential responses to loading that are unlikely to be captured in modern scaling techniques.

Recent work has addressed the flaws in scaling technique assumptions, particularly in the lower extremity. Roberts *et al.* [11] found that scaling male inversion injury moment data of the ankle overestimates female response, but scaling within a given sex (e.g. from 50^{th} to 5^{th} percentile female) was less problematic, albeit unnecessary as these techniques introduced more variation in the dataset. Roberts *et al.* argued that individual biomechanical characteristics, including bone geometry, are more indicative of injury probabilities than subject-level variables such as height and weight [11]. Patton *et al.* [12] found that males have 158% stronger bone in the femoral neck at matched stiffness values in females. Multiple studies have found that males have stronger long bones relative to body size than females resulting from sex-specific processes in how females versus males build and lose cortical bone tissue [13-14]. Jepsen *et al.* demonstrated structural differences in female femora that were fundamentally different from just a slender or smaller version of male femora [14].

R.L. Hunter is an Assistant Professor in the Division of Radiologic Sciences, and research faculty in Injury Biomechanics Research Center (614-292-2875, randee.hunter@osumc.edu). Karen Briley is a research scientist at the Wright Center of Innovation in Biomedical Imaging. Amanda Agnew is an Associate Professor in the Injury Biomechanics Research Center. All authors are affiliated with The Ohio State University

Additionally, sexual dimorphism in age-related changes in bone cross-sectional geometry, bone mineral density (BMD) and mechanical properties have been demonstrated [15-17]. Thus, simple assumptions concerning the ability of subject-level variables such as size, sex or even age to predict the injury risk of long bones should be re-evaluated. Therefore, it is crucial to quantify tibia geometric variation relative to subject-level variables utilized in establishing injury risk for target demographics (e.g. 5th percentile female). The purpose of this study was to quantify sex differences in tibia cortical bone morphometrics as they relate to age and body size.

II. METHODS

Samples

Left tibiae were excised from 128 fresh post-mortem human subjects (PMHS) ranging in age from 16 to 95 years (males) and 28 to 98 years old (females) (Table I). PMHS were considered representative of potential variation in medical histories and causes of death that could reasonably be expected in the modern population of the USA. Exclusionary criteria included any evidence of ante-mortem fractures (or fracture healing), metastases, or infections of the tibiae. Ex vivo tibiae were wrapped in normal saline-soaked gauze and stored at -20^{o}C.

TABLE I
SAMPLE SIZE DEMOGRAPHICS

Sex	Sample size	Age (mean ± std. dev)	Body Mass (kg)
Males	87	63.2 ± 14.1	72.2 ± 14.3
Females	41	63.4 ± 19.8	58.3 ± 14.1

Image Acquisition

Computed tomography (CT) scans were performed on a Philips Ingenuity 64-slice system using a validated methodology of optimized acquisition parameters (Table II). A QRM phantom with rods of known calcium hydroxyapatite densities (0–800 mg/cm^3) and a water-filled syringe were included in each scan. Reconstructions were completed using Philips clinical software at a centerline width of 800/2000 and iDose 3 protocol. Consistency in acquisition and reconstruction parameters was maintained across CT scans to facilitate quantifying bone morphometric data.

TABLE II
CT ACQUISITION PARAMETERS

Power (kV)	Current (mAs)	Slice thickness (mm)	Matrix size	In-plane resolution (mm)
120	262	0.67	1024x1024	0.335

Bone morphometric parameters

Quantitative CT (QCT) analyses of cortical bone were performed using the commercially available and validated SkyScan CTAn (Bruker) software package. The program allows for measurement, reorientation in x/y/z planes, and analysis of reconstructed DICOM images. Each tibia was reoriented relative to the medullary cavity and measured for total length from distal articular surface to the proximal tibial plateau (Fig. 1). Segment site locations were chosen to be comparable to previous work [18]. Individual volumes of interest (VOI) consisting of 10 slices centered at each segment site (38%, 50% and 66%) were isolated, resulting in 6.7 mm in the z-direction available for analysis (Fig. 1). Consistent greyscale thresholding values isolated the cortical bone within each VOI for quantification of morphometric parameters representing bone quantity (Tt.Ar, Ct.Ar, Ct.Th), distribution (I_{AP} and I_{ML}), robustness (Tt.Ar in relation to gross geometry of the bone) [18], and volumetric bone mineral density (vBMD), a commonly used proxy for material properties (Table III). The vBMD values were calculated using the known densities from the QRM phantom as well as water to create a calibration curve for each tibia. To account for variation in moment arm for each individual tibia, “body size” was calculated as total body mass (kg) multiplied by total tibia length (Bm*Le).

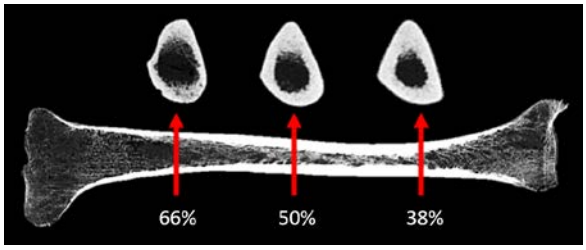


Fig. 1. Representative whole-bone CT scan with VOIs defined at 38%, 50% and 66% of total length.

TABLE III
QUANTIFIED MORPHOMETRIC DATA

Variable	Abbreviation (unit)	Description
Total area	Tt.Ar (mm^2)	Total cross-sectional area
Cortical area	Ct.Ar (mm^2)	Area between periosteal and endosteal borders
Cortical thickness	Ct.Th (mm)	Mean distance from periosteal to endosteal border
Robustness	- (mm)	Measure of whole bone geometry (Tt.Ar/length)
Area moment of inertia	I (mm^4)	Measure of resistance to bending (medial-lateral and anterior-posterior)
Volumetric bone mineral density	vBMD (mg/cm^3)	Calculated from calibration curves and averaged per VOI

Statistical Analysis

Two-sample t-tests were used to investigate sexual dimorphism in bone morphometric data. Sex-specific linear regressions were used to determine any age-related changes in tibia morphometrics and determine if, in this sample, males and females were gaining or losing bone through varying mechanisms. The effect of body size was quantified through linear regressions using both basic body mass (kg) and the composite measure Bm*Le. To determine if male and female tibiae were differentially affected by subject-level variables, ANCOVA analyses of slopes and y-intercepts for each regression were performed.

III. RESULTS

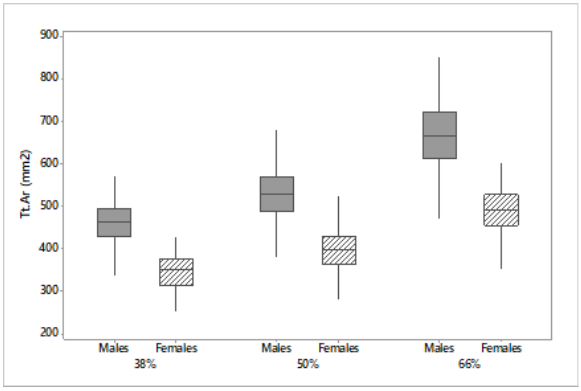
Sex Differences in the Tibia

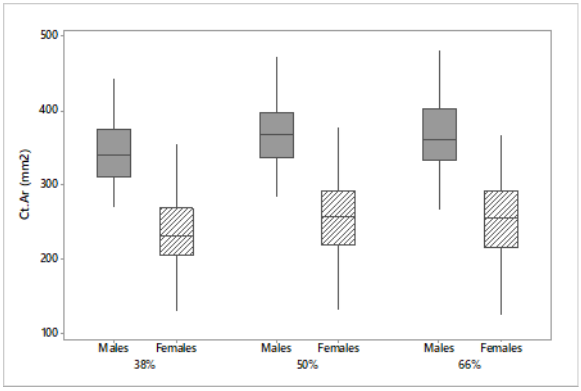
Males demonstrated significantly larger morphometrics at all VOIs compared to females (Table IV). Tt.Ar, I_{ML}, I_{AP} and robustness increased from distal (38%) to proximal (66%) in both sexes (Table IV, Fig. 2). Ct.Th demonstrated the opposite trend for both sexes with smaller values at 66% or closer to the knee joint. Although parameters quantifying cross-sectional bone mass and distribution as well as whole-bone geometry (robustness) exhibited marked sexual dimorphism, vBMD was not significantly larger in males (Table IV). The amount of overlap in the range of vBMD values between males and females at all VOIs in the tibia is demonstrated in Fig. 3.

TABLE IV
SEX DIFFERENCES IN TIBIA MORPHOMETRIC PARAMETERS

Parameter	Sex	Mean ± Std.Dev	Minimum	Maximum	p-value
38% Tt.Ar (mm^2)	Male	458.4±51.2	335.7	570.0	<0.001
	Female	347.2±46.2	254.5	472.7	
38% Ct.Ar (mm^2)	Male	340.9±45.7	179.8	443.2	<0.001
	Female	237.0±45.9	130.7	354.3	
38% I_{ML} (mm^4)	Male	22616±5323	9059	35369	<0.001
	Female	11917±3335	6112	22801	

38% I_{AP} (mm^4)	Male	11909±3037	5566	21367	<0.001
	Female	6678±2107	2347	12577	
38% Ct.Th (mm)	Male	5.1±0.7	2.6	6.6	<0.001
	Female	4.0±0.9	2.3	5.4	
38% Robustness (mm)	Male	1.2±0.1	0.8	1.4	<0.001
	Female	1.0±0.1	0.8	1.2	
38% vBMD (mg/cm^3)	Male	1207±44.1	1030.9	1307.2	0.17
	Female	1195±46.2	1093.8	1270.9	
50% Tt.Ar (mm^2)	Male	524.8±60.7	380.6	681.4	<0.001
	Female	395.1±51.7	279.7	526.0	
50% Ct.Ar (mm^2)	Male	367.8±50.5	195.3	495.7	<0.001
	Female	256.7±52.6	132.9	377.4	
50% I_{ML} (mm^4)	Male	30475±7177	12064	50130	<0.001
	Female	15809±4272	7732	27495	
50% I_{AP} (mm^4)	Male	14477±3876	6772	28106	<0.001
	Female	7925±2492	2493	15815	
50% Ct.Th (mm)	Male	4.9±0.7	2.6	6.2	<0.001
	Female	3.9±1.0	1.9	5.6	
50% Robustness (mm)	Male	1.4±0.2	0.9	1.7	<0.001
	Female	1.1±0.1	0.8	1.4	
50% vBMD (mg/cm^3)	Male	1198.6±43.4	1029.4	1300.6	0.20
	Female	1187.2±48.6	1077.7	1270.7	
66% Tt.Ar	Male	665.8±82.2	470.9	907.6	<0.001
	Female	494.2±64.5	354.1	643.4	
66% Ct.Ar	Male	365.6±54.9	181.4	518.4	<0.001
	Female	253.8±53.6	125.5	368.3	
66% I_{ML} (mm^4)	Male	44863±10670	13443	73478	<0.001
	Female	22907±6198	10532	37909	
66% I_{AP} (mm^4)	Male	18389±4891	7304	34805	<0.001
	Female	9680±2937	3144	19275	
66% Ct.Th (mm)	Male	3.8±0.7	2.0	5.2	<0.001
	Female	3.1±0.8	1.7	4.3	
66% Robustness (mm)	Male	1.8±0.2	1.1	2.2	<0.001
	Female	1.4±0.2	1.0	1.8	
66% vBMD (mg/cm^3)	Male	1160.5±45.9	1014.7	1263.1	0.52
	Female	1157.5±47.5	1062.5	1242.8	





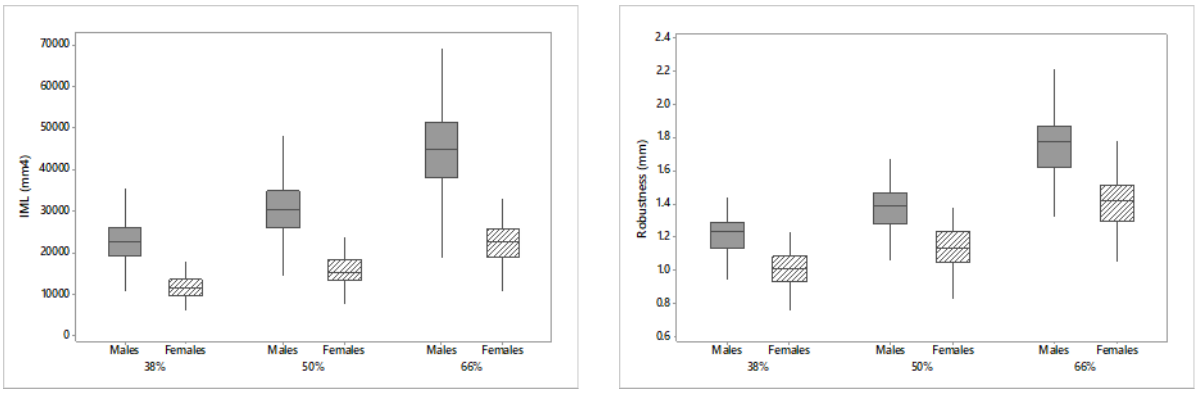


Fig. 2. Boxplots demonstrating significant sex differences.

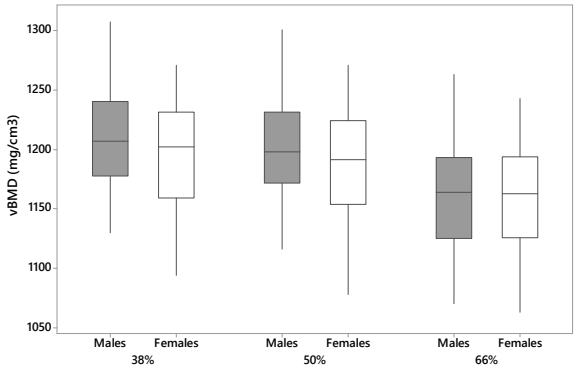


Fig. 3. Boxplot demonstrating no significant sex differences in vBMD at all VOIs.

Effects of Age on the Tibia

There were no significant differences in age distributions between males and females (p=0.94). Sex-specific linear regressions demonstrated varying patterns of parameters affected by age between males and females. For males, robustness increased significantly with age at 38% ($F(1,85)=7.8$, $p=0.006$), 50% ($F(1,85)=7.8$, $p=0.006$) and 66% ($F(1,85)=12.6$, $p=0.001$) VOIs (Fig. 4). Tt.Ar ($F(1,85)=6.6$, $p=0.012$) and I_{ML} ($F(1,85)=4.6$, $p=0.04$) also significantly increased with age in males, but only at the 66% VOI. Although age appeared to have significant effects on these tibia parameters in males, R^2 values remained low. Age explained only 7.7% of variation in robustness at both 38% and 50%. At the most proximal VOI (66%), age explained 12% of variation in robustness. Additionally, only 6.2% and 4.1% of variation in Tt.Ar and I_{ML}, respectively, was explained by age at the proximal (66%) VOI.

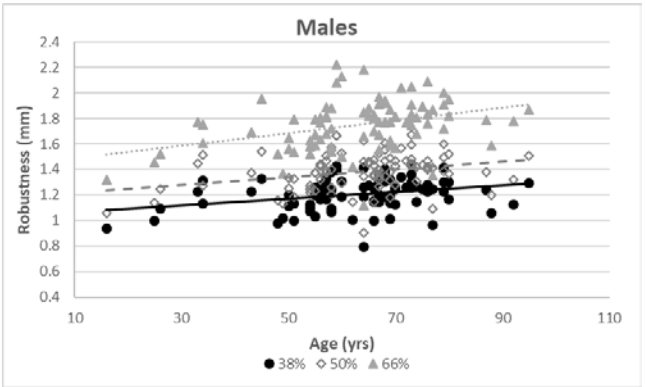


Fig. 4. Significant ($p<0.006$) increases in robustness with age in males.

Females demonstrated a consistent pattern of parameters affected by age throughout the tibia. Contrary to

males, significant declines occurred in Ct.Ar, Ct.Th and vBMD at all VOIs. For 38% Ct.Ar ($F(1,39)=6.1$, $p=0.018$), 50% Ct.Ar ($F(1,39)=6.3$, $p=0.017$) and 66% Ct.Ar ($F(1,39)=5.63$, $p=0.023$), age was only able to predict between 10.4% and 11.7% of variation, suggesting weak relationships similar to those found in males. However, both Ct.Th and vBMD were more sensitive to age-related changes. Ct.Th at 38% ($F(1,39)=11.7$, $p=0.002$), 50% ($F(1,39)=12.0$, $p=0.001$) and 66% ($F(1,39)=11.2$, $p=0.002$) decreased significantly with age, with R^2 values ranging from 21.0% to 21.6%. Lastly, the strongest effects of age were found in females in vBMD, explaining up to 33.4% of variation (66% site); whereas 25.9% and 26.2% of variation in 38% and 50% vBMD, respectively, was explained by age (Fig. 5). Although robustness demonstrated increasing trends with age in females as in males, these relationships were not significant ($p>0.8$).

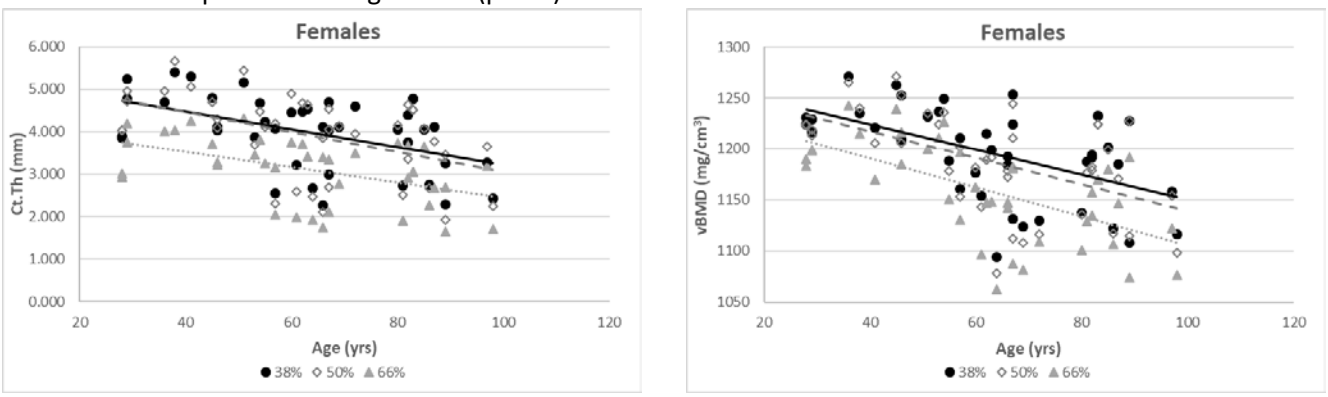
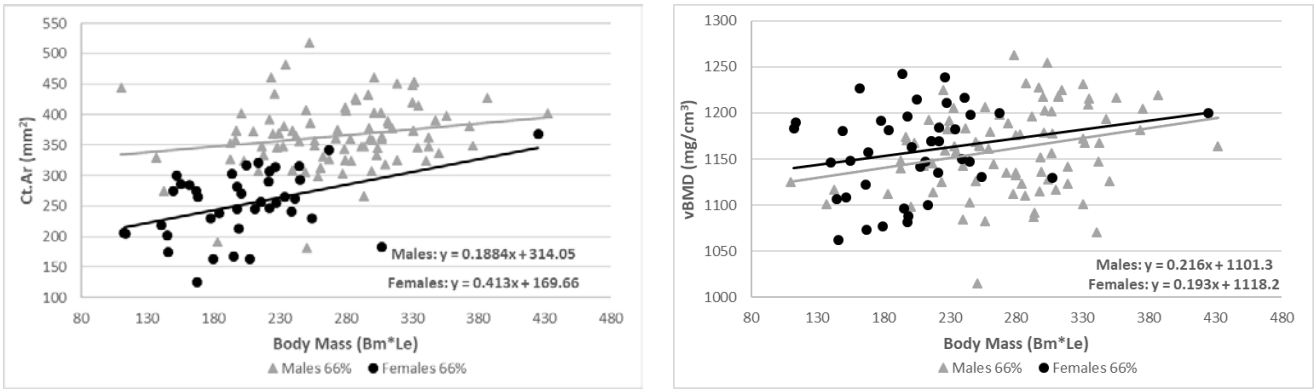


Fig. 5. Significant decreases in Ct.Th ($p<0.002$) and vBMD ($p<0.002$) with age in females only.

Effects of Body Size on the Tibia

Despite its weight-bearing nature, few parameters in males appeared to be sensitive to body mass. Simple body mass (kg) regressions against morphometrics did not predict any measures of bone quantity, distribution, or whole-bone geometry ($p>0.05$). In males, however, vBMD increased significantly with body mass at 38% ($F(1,85)=5.4$, $p=0.02$), 50% ($F(1,85)=6.6$, $p=0.01$) and 66% ($F(1,85)=7.22$, $p=0.009$) VOIs. R^2 values increased from distal to proximal in the tibia (4.9–6.8%). Accounting for the length of the tibia in a composite variable for body mass (Bm*Le) demonstrated significant relationships with Ct.Ar and vBMD in males. At all VOIs, Ct.Ar and vBMD increased significantly with Bm*Le, but the relationships remained weak with R^2 values ranging from only 3.4% to 6.7%. In addition to Ct.Ar and vBMD, I_{AP} at 66% ($F(1,85)=7.09$, $p=0.009$, $R^2=6.2\%$) increased significantly with Bm*Le but continued to demonstrate a weak relationship in males. Female tibiae were more sensitive to increasing mass as all morphometrics increased significantly ($p<0.01$) with both measures of body mass (kg and Bm*Le) at all sites, with the exception of Ct.Th and vBMD. Bm*Le demonstrated stronger relationships with all morphometrics in females than simple body mass alone, and these comparisons are reported in Table V.



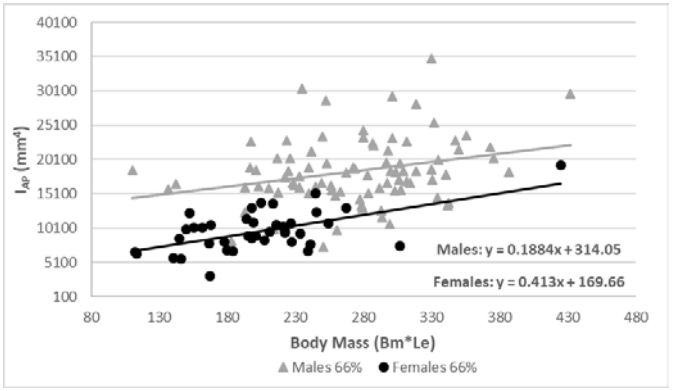


Fig. 6. Significant increases with age at 66% sites for both males and females. Trend lines demonstrate no significant differences in slope (p>0.08), but significantly smaller y-intercepts for females (Ct.Ar, p=0.001; I_{AP}, p=0.01).

TABLE V
FEMALES ONLY LINEAR REGRESSION WITH BM*LE

Parameter	F-value (1,39)	p-value	R^2
38% Tt.Ar	19.51	<0.001	0.32
38% Ct.Ar	14.12	0.001	0.25
38% I_{ML}	25.35	<0.001	0.38
38% I_{AP}	15.74	<0.001	0.27
38% Ct.Th	3.30	0.077	0.05
38% Robustness	10.46	0.002	0.19
38% vBMD	2.54	0.12	0.04
50% Tt.Ar	17.34	<0.001	0.29
50% Ct.Ar	9.67	0.003	0.18
50% I_{ML}	16.80	<0.001	0.28
50% I_{AP}	19.65	<0.001	0.32
50% Ct.Th	2.33	0.14	0.03
50% Robustness	8.75	0.005	0.16
50% vBMD	2.44	0.13	0.03
66% Tt.Ar	13.77	0.001	0.24
66% Ct.Ar	8.36	0.006	0.16
66% I_{ML}	14.57	<0.001	0.25
66% I_{AP}	19.92	<0.001	0.32
66% Ct.Th	3.10	0.09	0.05
66% Robustness	6.59	0.014	0.13
66% vBMD	2.01	0.16	0.02

To determine if Ct.Ar, vBMD, or I_{AP} experienced similar rates of change with Bm*Le, the slopes of male and female regression lines were compared (Fig. 6). For comparisons between sexes in the effects of body size on Ct.Ar, trendline slopes were not significantly different (p>0.08) at any VOI, but the y-intercepts for females were significantly lower than males (p<0.001), indicating that for any given body size, Ct.Ar is smaller in females. A similar analysis for vBMD revealed no significant differences in slope (p>0.51) or y-intercept (p>0.60) between sexes at any VOI, suggesting similar mechanisms for changes in this parameter with body size. Lastly, at 66% VOI there was no significant difference (p=0.6) in slopes for I_{AP}, but females exhibited a significantly smaller y-intercept (p=0.01).

IV. DISCUSSION

Significant sex-specific responses to the effects of age and body size demonstrated here provide further support to the assertion from recent studies that females are not just a smaller version of males [11][14]. The data presented here suggest that males and females gain and lose bone as well as experience the systematic effects of age and body size differentially. Sexual dimorphism in tibia morphometric data has been reported in previous studies [13][15-17] and is supported here in all parameters except vBMD. Contrarily, Walsh *et al*. [15] reported smaller cortical vBMD in young males compared to females. However, in a sample ranging in age from 26 to 86 years, Kaji *et al*. [19] found larger vBMD values in males in the distal radius. Riggs *et al*. [20] found 35–42% larger bone areas across the skeleton in males, including significantly larger vBMD. The lack of significant differences in vBMD between sexes found in this study suggests that this parameter may not be appropriate in encompassing the level of variation present in loading response and differential injury risk. Although sexual dimorphism in bone quantity and distribution has been established, it is crucial to investigate further if subject-level variables impact larger male and smaller female tibia in a manner that would justify current scaling assumptions.

Differential effects of age on tibia parameters were found in this sample despite no significant differences in age distribution between sexes. In the current study, the nature of relationships between tibia variables and age reflected sex-specific patterns. Age demonstrated overall weaker relationships in males than in females, supporting recent work questioning the relevance of chronological age in predicting skeletal injury [21]. However, the relationship between age and bone morphometric data is not consistent across previous work. Patton *et al*. [12] found age- and sex-dependent relationships between stiffness and strength in the femur, suggesting structure-function link is altered by varying mechanisms in males versus females. Additionally, Milovanovic *et al*. [17] found differential effects of age on female compared to male distal tibiae, with females experiencing stronger response to age-related changes in Ct.Ar, vBMD and Ct.Th than males. Similar to [17], the females in this study demonstrated stronger inverse relationships in these variables with age than males. Dalzell *et al*. [16] also found the greatest relative effects of age on Ct.Th and vBMD in the tibia for females. Interestingly, the males in this study demonstrated very few but direct relationships with age, contrary to other work where cortical bone morphometrics tend to decline with age [16-17][20-21]. Here, only robustness was significantly affected by age throughout the entirety of the tibia in males, demonstrating significant increase ($p<0.05$). Although significant increases in Tt.Ar (also reflected in robustness) attributed to periosteal apposition or expansion have been reported in both sexes with age [16][22], this study found evidence in males only. The decline in cortical morphometrics and vBMD reported elsewhere in males [16-17][22] was not supported here. None of the measures of bone quantity, distribution, whole bone geometry, or vBMD exhibited similar relationships with age for analysis of differential rates of change between sexes.

The effect of body size was investigated using both simple body mass (kg) as well as a composite variable Bm*Le. Body size, as measured by either variable, did not seem to affect male tibia to the extent that female tibia parameters varied with mass (kg) or Bm*Le. Previous work in both weight-bearing and non-weight-bearing skeletal elements has demonstrated significant response in morphometric parameters to variation in body size. Schlecht *et al*. [13] reported females have more slender bones than are expected for their body size or bone size. They also demonstrated increasing robustness with body size (Bm*Le) in all elements. In this study, although Bm*Le was a better predictor of tibia parameters in both sexes, males did not demonstrate an increase in robustness. Despite the weight-bearing nature of the tibia and body mass, ranging from 28.1 kg to 109.8 kg, only Ct.Ar and vBMD weakly increased with body size. Conversely, all parameters in females (ranging from 34.1 kg to 110.2 kg) were significantly affected by body size, suggesting a higher sensitivity present that may have been mitigated in males by other factors. For Ct.Ar and vBMD, which both demonstrated increasing trends with body size, comparison of slopes and y-intercepts indicated no significant differences in rates of change between sexes but a significantly smaller y-intercept for females in Ct.Ar. These differential patterns suggest a more complex relationship between body size and the tibia that is not captured in current anthropometric measures. Historically, the sexual dimorphism in bone size was largely attributed to the mechanical influences of skeletal muscle; however, recent work has found this to be only one facet of the relationship between overall body and muscle size and bone functional adaptation [23-24]. The importance of the secretory role of both muscle and bone, which is regulated by a multitude of factors including but not limited to mechanical forces, may help elucidate the biological underpinnings of these sex differences.

Ultimately, as Roberts *et al.* [11] argued, these data support local variation in bone morphometric parameters that may drive biomechanical response beyond gross anthropometry.

The contribution of geometric variation on injury tolerances at different locations along the length of the tibia have been investigated as they relate to injury risk prediction [25-26]. Mo *et al.* [25] found that fracture moment of tibia varied largely between proximal and distal 1/3 of the tibia, and injury tolerance developed at mid-shaft may not represent the entirety of the tibia due to variances in cortical geometry. Differences in morphometrics and vBMD across tibia VOIs was not directly investigated here but have been reported previously [27]. The proximal tibia appears to be slightly more sensitive to changes in age and body mass, as evidenced by the addition of significantly affected parameters here, especially in males. The biological relevance of these variations and implications for differential fragility and fracture risk across the tibia will be elucidated following future dynamic experimental testing of the tibiae explored in this study.

V. CONCLUSIONS

This study includes a large sample representative of the realistic amount of variation in tibia geometry found in the population. Females do exhibit smaller measures of bone quantity and distribution than males, a trend not reflected in vBMD. However, these data, demonstrating dissimilar impacts of age and body size on tibia morphometrics between sexes, suggest current scaling methods from males to females may be inappropriate to predict injury. Development of injury risk curves for tibia fractures must take into account the fundamentally different biological influences in females not present in males and attempt to quantify the factors underpinning local biomechanical response (such as geometric variation) to loading.

VI. ACKNOWLEDGEMENTS

We are grateful to the anatomical donors and their families, without whom this research would not have been possible. Thanks to Michael Knopp and the Wright Center for Innovation in Biomedical Imaging, especially James Ellis. We would like to thank the faculty, staff and students of the Injury Biomechanics Research Center.

VII. REFERENCES

[1] Centers for Disease Control, National Center for Injury Prevention and Control (2019) Web-based Injury Statistics Query and Reporting System (WISQARS) online. Accessed 21 March 2019.

[2] National Highway Traffic Safety Administration (2018) Traffic Safety Facts 2016 data - Pedestrians. DOT HS 812 493. (2018-revised). *NHTSA*, Washington D.C., USA.

[3] Mizuno, Y. and Ishikawa, H. (2001) Summary of IHRA Pedestrian safety working group. National Highway Traffic Safety Administration (2001-06-0136).

[4] Carter, E. L., Neal-Sturgess, C. E., Hardy, R. N. (2009) APROSYS in depth database of serious pedestrian and cyclist impacts with vehicle. *International Journal of Crashworthiness,* **13**(6): pp. 629–42.

[5] Yang, J. K. (2005) Review of injury biomechanics in car-pedestrian collisions. *International Journal of Vehicle Safety,* **1**: pp. 100–17.

[6] Paas, R., Huber, R., Wilsmann, J., Martinez von Bülow, Kompaß, K. (2018) Pedestrian leg injury distribution in German in-depth accident study for leg impactor development. In: *Proceedings of the 2018 International IRCOBI Conference*, Athens, Greece, pp. 305–6.

[7] Kerrigan, J., *et al*. (2004) Tolerance of the human leg and thigh in dynamic latero-medial bending. *International Journal of Crashworthiness,* **9**(6): pp. 607–23.

[8] Yamada, H. (1970) Strength of Biological Materials. *Williams and Wilkins*, Baltimore, USA.

[9] Mather, B. S. (1968) Variation with age and sex in strength of the femur. *Medical and Biological Engineering,* **6**: pp. 129–32.

[10] Eppinger, R. H., Marcus, J. H. and Morgan, R. M. (1984) Development of dummy and injury index for NHTSA's thoracic side impact protection research program SAE. SAE Technical Paper (No.840885).

[11] Roberts, C., Forman, J. and Kerrigan, J. (2018) Injury risk functions for 5th percentile females: ankle inversion and eversion. In: *Proceedings of the 2018 International IRCOBI Conference*, Athens, Greece, pp. 702–17.

[12] Patton, D., *et al*. (2019) The relationship between whole bone stiffness and strength is age and sex dependent. *Journal of Biomechanics,* **83**: pp. 125–33.

[13] Schlecht, S., Bigelow, E. and Jepsen, K. J. (2015) How does bone strength compare across sex, site, and ethnicity? *Clinical Orthopedics and Related Research,* **473**: pp. 2540–47.

[14] Jepsen, K. J., Bigelow, E., Schlecht, S. (2015) Women build long bones with less cortical mass relative to body size and bone size compared to men. *Clinical Orthopedics and Related Research,* **473**(8): pp. 2530–39.

[15] Walsh, J. S., Paggiosi, M. A. and Eastell, R. (2012) Cortical consolidation of the radius and tibia in young men and women. *Endocrine Research,* **97**(3): pp. 3342–8.

[16] Dalzell, N., *et al*. (2009) Bone microarchitecture and determinants of strength in the radius and tibia: age related changes in a population-based study of normal adults measured with pQCT. *Osteoporosis International,* **20:** pp. 1683-94

[17] Milovanovic, P., *et al*. (2015) Age and sex specific bone structure patterns portend bone fragility in radii and tibiae in reaction to osteodensitometry. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, **70**: pp. 1269-75

[18] Jepsen, K. J., *et al*. (2011) Biological constraints that limit compensation of a common skeletal trait variant lead to inequivalence of tibial function among health young adults. *Journal of Bone and Mineral Research,* **26**(12): pp. 2872–85.

[19] Kaji, H., *et al*. (2005) Effects of age, grip strength, and smoking on forearm vBMD and bone geometry by pQCT: comparisons between female and male. *Endocrine Journal,* **52**(6): pp. 659–66.

[20] Riggs, B. L., *et al*. (2004) Population-based study of age and sex differences in bone volumetric density, size, geometry, and structure at different skeletal sites. *Journal of Bone and Mineral Research,* **19**(12): pp. 1945–54.

[21] Agnew, A., *et al.* (2018) Sources of variability in structural bending response in pediatric and adult human ribs in dynamic frontal impacts. *Stapp Car Crash Journal* **62:** pp. 119-92.

[22] Jepsen, K. J. and Andarawis-Puri, N. (2012) The amount of periosteal apposition required to maintain bone strength during aging depends on adult bone morphology and tissue modulus degradation rate. *Journal of Bone and Mineral Research,* **27**(9): pp. 1916–26.

[23] Li, G., *et al.* (2019) Muscle-bone cross-talk and potential therapies for sarco-osteoporosis. *Journal of Cellular Biochemistry*, pp. 1-12.

[24] Bonewald, L. (2019) Use it or lose it to age: a review of bone and muscle communication. *Bone* **120:** pp. 212-18

[25] Mo, F., Arnoux, P. J., Jure, J. J., Masson, C. (2012) Injury tolerance of tibia for car-pedestrian impact. *Accident Analysis and Prevention,* **46**: pp. 18–25.

[26] Ivarsson, B. J., *et al*. (2004) Dynamic response corridors and injury thresholds of the pedestrian lower extremities. In: *Proceedings of the 2004 International IRCOBI Conference*, Grax, Austria, pp. 171–91.

[27] Hunter, R. L., Murach, M. M., Briley, K. C., Agnew, A. M. (2017) Preliminary investigation into the co-variation of cortical geometric properties and vBMD along the length of the tibia. In: *Proceedings of the 2017 International IRCOBI Conference*, Antwerp, Belgium, pp. 711–12.