Investigation of Sex-specific Effects on Variation in Cortical Bone Morphometrics of the Radius

Randee L. Hunter, Zachary Haverfield, Amanda M. Agnew

Abstract Persistently high frequency of forearm fractures in frontal and side impacts coupled with their long-term deleterious effects demands an in-depth understanding of variation in skeletal response to loading. Previous work has highlighted the differential impact of subject-level variables on bone quality between males and females. The purpose of this study was to evaluate effects of sex on variation in cortical bone morphometrics of the radius. Quantitative computed tomography analyses were performed on n=150 ex vivo post-mortem human subject radii from 96 males and 54 females. Morphometrics that represent bone quantity, cross-sectional distribution, whole-bone geometry, and mineralisation were quantified in the radius diaphysis. Females demonstrated significantly smaller cortical morphometric parameters ($p<0.003$) with the exception of whole-bone geometry and mineralisation ($p>0.81$). Sex-specific linear regressions demonstrate significant increases in some parameters with age in males ($p<0.004$) however, the amount of bone and mineralisation decreased with age in females ($p<0.001$). Females appeared to be more sensitive to changes in height and demonstrated positive relationships in more morphometrics than males. Multivariate regressions analysing combined effects of age and height explained more variation in morphometrics than age or height alone. The sex-specific effects of subject-level variables on cortical bone indicate varying mechanisms of bone functional adaptation that should be accounted for in injury risk predictions rather than body size-based scaling techniques.

Keywords Cross-sectional geometry, cortical bone, radius, sex-based differences, upper extremity.

I. INTRODUCTION

Despite newly developed safety mechanisms that have successfully resulted in decreased injury risk to many body regions, upper extremity injuries remain an issue in motor vehicle crashes. Upper extremity fracture (UEF) patterns vary with many factors including principal direction of impact, crash severity, and restraint use [1]; yet, multiple studies have highlighted the consistently high risk for injury in this body region. Forman et al. [2] found that although prevalence of lower extremity injury in frontal collisions decreased with newer model year vehicles, arm/forearm and hand/wrist fractures remained the same between old vs. new. Furthermore, UEF were the most prevalent AIS 2+ (Abbreviated Injury Scale) injury in newer model vehicles [2]. Weaver et al. [3] also demonstrated risk for AIS 2 injury in belted occupants was highest in the upper (and lower) extremities; more specifically, fractures to the radius ranked in the top third of injury risk for belted occupants while unbelted occupants retained an overall higher risk for radius and ulnar fracture. Fractures of the forearm bones were attributed mainly to interactions with a component of the vehicle interior in both frontal and side impacts [4] while others have investigated the contribution of side air bag deployment to forearm fractures [5-7]. Regardless of crash scenarios, of the 12,754 UEF in the Israel National Trauma Registry, the radius was the most frequently fractured (22%) in car occupants (21%), motorcycle collisions (26%), and bicycle collisions (24%) [8]. Radius fractures, especially to the cortical bone of the diaphysis, can result in suboptimal outcomes and decreased health related quality of life especially in females [9]. Thus, improving safety mechanisms to prevent radius fractures is crucial and should be achieved in the context of sex-specific understanding of bone functional adaptation, defined as the processes by which bone coordinates morphological and material properties due to varying systemic and mechanical environments [see reference [10] for review], driving differential response to loading scenarios.

Injury tolerance has previously been investigated in the distal [11] and cortical diaphysis [12] of the radius but with conflicting results as to relationships between strength and bone morphometric parameters, e.g., bone mineral density, amount of bone, etc. Post-mortem Human Subject (PMHS) whole forearm studies focused on 5^{th} female [11] and 50^{th} male [13] occupants may not capture the variation in bone quality driving the response to loading. Scaling these data based upon techniques that assume similar but size-dependent geometric properties [14] likely obscure crucial sex-specific factors that influence strength in the radius. In other body regions, e.g., ankle joint, size based scaling techniques have overestimated female response [15].

Sex-specific differences in cortical bone functional adaptation to age, body size, altered mechanical loading environment, etc., have tangible effects on whole bone strength. Hunter et al. [16] found significant differences between the sexes along the tibia cortical diaphysis with respect to age and body size, indicating that females are not simply a smaller version of males but adapt to changes via differing mechanisms than males. These patterns of biological differences between the sexes in skeletal development, aging, and the maintenance of strength throughout life have been demonstrated across the skeleton [17-20] but on small sample sizes and in some cases, restricted age ranges. Re-evaluating the ability of subject-level variables to predict response to loading in the radius will aide in more comprehensive understanding of sex-based differences in mechanisms of bone functional adaptation and resulting whole bone strength. Therefore, the purpose of this study was to quantify the differential effects of sex on variation in cortical bone morphometrics, a characterisation of bone functional adaptation processes, of the radius with respect to the target demographics used to inform injury prediction models.

II. METHODS

Samples

Bilateral radii were excised from 150 PMHS ranging in age from 24 to 96 years (males) and 28 to 98 years old (females) from a wide range of body sizes (Table I). Radii were excluded if any visible signs of fracture, fracture healing, periosteal reactions (infections) or lesions (sclerotic or lytic) of the bone were found. *Ex vivo* radii were wrapped in normal saline-soaked gauze for storage at -20^{o}C. To remove any potential biases due to handedness, which is unknown for these individuals, and due to the lack of side differences in any variable when bilateral radii were compared for this sample ($p>0.09$), the sample was randomised such that only one radius was chosen to represent each individual (n=150 total radii for analysis).

TABLE I
SAMPLE SIZE DEMOGRAPHICS

Sex	Sample size	Age (mean ± std. dev)	Height (cm)	Weight (kg)
Males	96	63.8 ± 13.9	178.7 ± 7.2	74.8 ± 13.5
Females	54	64.0 ± 17.1	164.2 ± 6.8	60.7 ± 14.3

Image Acquisition

All computed tomography (CT) scans were acquired using a validated methodology on a Philips Ingenuity 64-slice system with consistent acquisition parameters (120 kV; 262 mA; 1024x1024 matrix; 0.67mm slice thickness). Although acquired on a clinical CT system, the resulting in-plane resolution (0.167mm) was much higher than a typical whole body CT examination (~0.8mm-1.26mm) allowing for high resolution visualisation of the cortex. A Bone Density Calibration Phantom (BDX/6-QRM, Möhrendorf, Germany) was included with each scan to facilitate synchronous bone mineral density calibrations. Reconstructions were completed using Philips iDose 3 clinical protocol at a centreline of 800 and window width of 2000 which determine the brightness and contrast, respectively, of the reconstructed image greyscale. The BDC/6-QRM phantom included rods of known calcium hydroxyapatite densities (0–800 mg/cm^3) so that scan-specific Hounsfield Units (HU) could be calibrated to volumetric bone mineral density (vBMD) values using the resulting calibration curve. Consistency in acquisition and reconstruction parameters was maintained across all CT scans to facilitate comparable bone morphometric data.

Bone Morphometric Parameters

High resolution quantitative CT (QCT) analyses of cortical bone were performed using the commercially available and validated SkyScan CTAn (Bruker) software package as previously described in [16]. Each radius was measured for length from the proximal articular (head) to distal articular surfaces (excluding the styloid process). Volumes of interest (VOIs) at the 30% (relative to the distal articular surface) and 50% sites included 10 slices or 6.7mm of bone in the z-direction for all morphometric analyses (Fig. 1). To analyse cortical bone, greyscale thresholds (175-255) were consistently applied across all samples. SkyScan CTAn quantified cortical bone morphometrics (Table II) that represent bone mass or quantity of bone (Tt.Ar, Ct.Ar, %Ct.Ar, Ct.Th), distribution of bone (area moment of inertia, I), whole-bone geometry (robustness) and cortical vBMD which is typically used

as a proxy for material properties in non-invasive imaging [21,22]. Due to the lack of relationship between PMHS body weight and any morphometric for the non-weight bearing radius ($p>0.05$), weight was not included in analyses but was reported in Table I to demonstrate the range represented in this sample. However, previous work has identified body height as a significant predictor of radius strength [23] and injury risk for small females [11] and thus, was included here as the relevant measurement of *body size*.

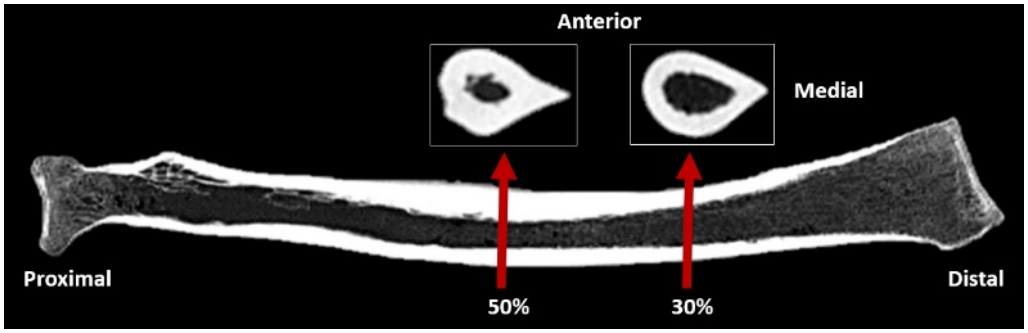

Fig. 1. Representative whole-bone CT scan of the radius with VOIs defined at 30% and 50% of total length (measured from the distal articular surface).

TABLE II
CORTICAL BONE MORPHOMETRIC PARAMETERS

Category	Variable	Abbreviation (unit)	Description
Bone quantity	Total area	Tt.Ar (mm^2)	Total cross-sectional area
	Cortical area	Ct.Ar (mm^2)	Area between periosteal and endosteal borders
	Relative cortical area	%Ct.Ar	Normalised area for cross-sectional size (Ct.Ar/Tt.Ar)
	Cortical thickness	Ct.Th (mm)	Mean distance from periosteal to endosteal border calculated by the annular (derived) method [24]
Whole-bone geometry	Robustness	- (mm)	Index of longitudinal and transverse growth (Tt.Ar/length)
Distribution of bone	Area moment of inertia	I (mm^4)	Measure of resistance to bending (medial-lateral and anterior-posterior)
Mineralisation proxy	Volumetric bone mineral density	vBMD (mg/cm^3)	Calculated from scan-specific calibration curves from QRM phantom and using threshold values to isolate cortical bone

Statistical Analysis

Independent sample t-tests were used to investigate differences in radius cortical bone morphometrics between males and females at both the 30% and 50% sites. Hedge's g was used to determine the standardised magnitude of differences or effect size of sex, corrected for sample size, on radius morphometrics. Univariate sex-specific linear regressions were used for age and height to determine if these subject-level variables could predict radius cortical bone morphometrics. To assess if male and female radii were differentially affected by subject-level variables, ANCOVA analyses of slopes and y-intercepts for regressions demonstrating similar trends with age or height between sexes were performed. Finally, multivariate regressions were used to determine the combined sex-specific effects of age and height on cortical morphometric parameters. Alpha level was set *a priori* at 0.01.

III. RESULTS

Sex Differences in the Radius Cortical Bone Morphometric Parameters

Males demonstrated significantly larger morphometrics at both sites compared to females with the exception of vBMD (Table III; Fig. A1). The standardised effect size (Hedge's g) for Tt.Ar, Ct.Ar, I_{ML}, I_{AP} and robustness were large with males at least two standard deviations greater than females. Ct.Th showed a smaller magnitude of difference (Table III) indicating a lesser degree of sexual dimorphism. To investigate whether the normalised amount of cortical bone at each site was markedly different between sexes rather than simply a magnitude of size difference, relative cortical area (%Ct.Ar) was compared. Significantly higher values of %Ct.Ar in males indicated that for any given Tt.Ar, males have a larger proportion of cortical area (more bone mass) than females (Fig. 2). Despite more bone mass and differing whole bone geometry (robustness) and distribution (I_{ML} and I_{AP}), vBMD was not significantly different between sexes (Table III) and demonstrated a narrow range of variation with less than 200 mg/cm^3 difference between minimum and maximum values for both sites and sexes.

TABLE III
SEX DIFFERENCES IN RADIUS MORPHOMETRIC PARAMETERS

Site	Parameter	Sex	Mean	Std.Dev	Min	Max	p-value	Hedge's g
30%	*Tt.Ar (mm^2)*	Male	134.9	18.3	92.9	186.6	<0.001	2.64
		Female	90.4	13.8	63.2	127.9		
	Ct.Ar (mm^2)	Male	93.5	14.8	53.5	137.9	<0.001	2.38
		Female	57.5	15.7	24.7	84.1		
	%Ct.Ar	Male	0.70	0.10	0.39	0.87	0.003	0.60
		Female	0.63	0.14	0.37	0.85		
	I_{ML} (mm^4)	Male	1040.9	259.9	494.4	1851.3	<0.001	2.64
		Female	450.9	136.1	181.8	756.1		
	I_{AP} (mm^4)	Male	1692.4	490.1	925.0	3132.5	<0.001	2.29
		Female	715.5	277.3	215.9	1297.0		
	Ct.Th (mm)	Male	2.6	0.5	1.3	3.6	<0.001	1.3
		Female	1.9	0.6	0.9	3.0		
	robustness (mm)	Male	0.55	0.07	0.41	0.73	<0.001	2.1
		Female	0.41	0.06	0.30	0.56		
	vBMD (mg/cm^3)	Male	1114.4	27.1	1043.3	1183.1	0.99	0
		Female	1114.4	34.2	1048.9	1177.6		
50%	*Tt.Ar (mm^2)*	Male	138.4	17.4	93.5	194.5	<0.001	2.73
		Female	95.0	12.7	68.4	126.4		
	Ct.Ar (mm^2)	Male	105.3	17.0	61.1	159.6	<0.001	2.35
		Female	64.9	17.5	27.5	101.3		
	%Ct.Ar	Male	0.76	0.10	0.46	0.91	<0.001	0.66
		Female	0.68	0.15	0.34	0.89		
	I_{ML} (mm^4)	Male	1199.0	277.0	572.0	2103.5	<0.001	2.9
		Female	505.2	150.1	217.5	960.7		
	I_{AP} (mm^4)	Male	1932.1	585.6	941.4	4358.3	<0.001	2.06
		Female	891.0	311.6	301.7	1709.4		
	Ct.Th (mm)	Male	2.9	0.6	1.4	3.9	<0.001	1.27
		Female	2.1	0.7	0.9	3.3		
	robustness (mm)	Male	0.57	0.07	0.42	0.75	<0.001	2.16
		Female	0.43	0.05	0.32	0.56		
	vBMD (mg/cm^3)	Male	1103.0	29.6	1022.2	1165.5	0.81	0.06
		Female	1105.0	41.3	1015.0	1173.9		

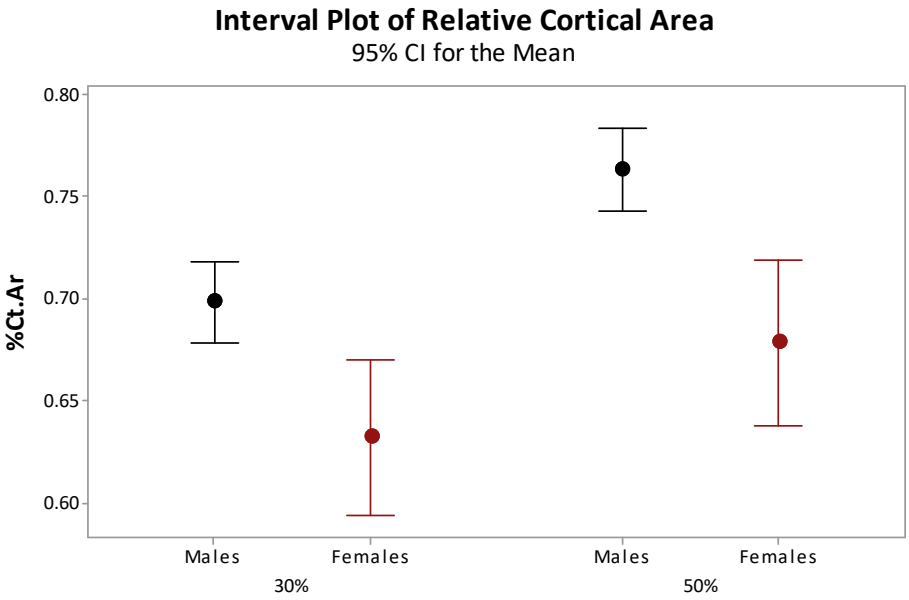

Fig. 2. After normalising by Tt.Ar (i.e., bone size), males demonstrated significantly more cortical bone (Ct.Ar) per site than females (p<0.003).

Effects of Age on the Radius

There were no significant differences in age distribution between males and females (p=0.98) in this sample. Univariate regressions indicated sex-specific trends with age in some morphometric parameters (Figs. 3 and 4; Table IV; Table A1), suggesting differential bone functional adaptation patterns for age between males and females. At both the 30% (Fig. 3) and 50% (Fig. A3) sites, males exhibited increases in Tt.Ar (and subsequently robustness) implying significant periosteal apposition likely to compensate for age-related bone loss on the endosteal border that typically occurs with increasing age [25]. This mechanism of adaptation is further supported by the significant decreases in Ct.Th (p<0.001; R^2=13.2%) and %Ct.Ar (p<0.001; R^2=16.7%) but only at the 30% site (Fig. 4). Females exhibited significant decreases in measures of bone quantity (Ct.Ar, Ct.Th, and %Ct.Ar) at both sites but, unlike males, no relationship between age and Tt.Ar or robustness (p>0.63) (Fig. 3; Fig. A3; Table AI) were found. For both sexes, neither I_{ML} nor I_{AP} were significantly associated with age in (Fig. A2; Fig. A3; Table AI). vBMD was the only parameter that significantly declined with age in both sexes at both the 30% (Fig. 4) and 50% (Fig. A4) sites. Overall, age was able to explain more variation in all parameters for females (R^2=20.0-34.9%) than males (R^2=5.2-16.7%) in both sites with consistently higher R^2 values at the more distal 30% site (Table AI).

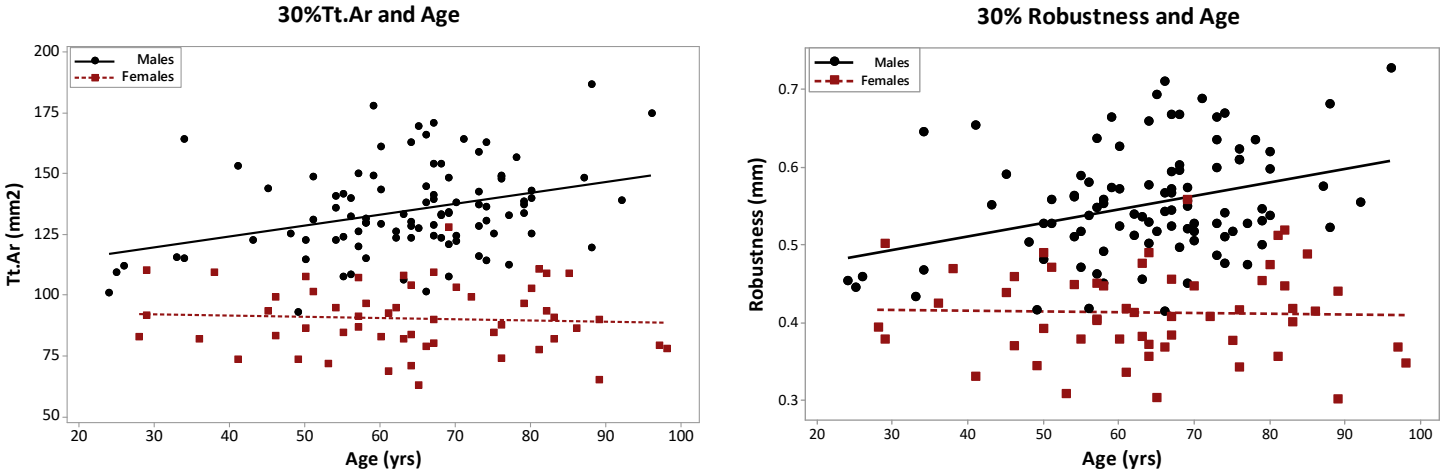

Fig. 3. Significant increases in Tt.Ar (p=0.001; R^2=11.3%) and robustness (p=0.001; R^2=11.5%) with age in males but not females (p=0.63 and 0.87, respectively) at the 30% sites.

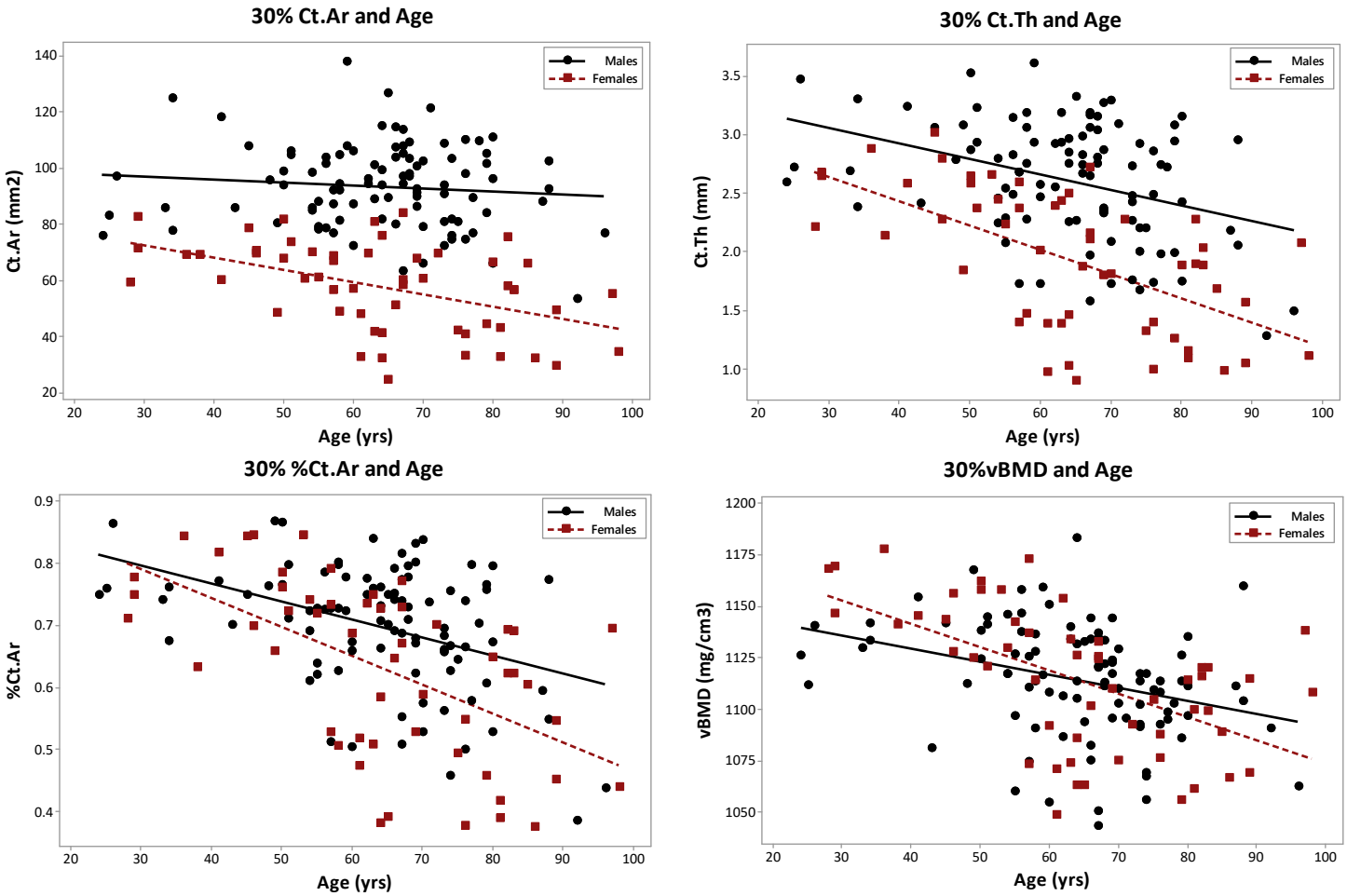

Fig. 4. Significant decreases in Ct.Ar for females at the 30% site (females $p<0.001$; R^2=22.7%, males $p=0.35$). Ct.Th ($p<0.001$; females R^2=34.9%, males R^2=13.2%), %Ct.Ar ($p<0.001$; females R^2=32.3%, males R^2=16.7%), and vBMD ($p<0.002$; females R^2=24.8%, males R^2=10.4%) decreased with age in both sexes at the 30% site.

TABLE IV
SUMMARY SEX-SPECIFIC LINEAR REGRESSION RELATIONSHIPS* WITH AGE

	30%		50%	
	Males	**Females**	**Males**	**Females**
Tt.Ar	Increase	No change	Increase	No change
Ct.Ar	No change	Decrease	No change	Decrease
%Ct.Ar	Decrease	Decrease	No change	Decrease
I_{ML}	No change	No change	No change	No change
I_{AP}	No change	No change	No change	No change
Ct.Th	Decrease	Decrease	No change	Decrease
Robustness	Increase	No change	Increase	No change
vBMD	Decrease	Decrease	Decrease	Decrease

*Relationship trends are reported based on statistical significance

ANCOVA tests of the rate of change (slope) and y-intercept (constant) between males and females were performed only for parameters that exhibited significant and similar trends with age i.e., %Ct.Ar, Ct.Th, and vBMD (Table IV). There were no significant differences in the rate of change for 30% Ct.Th ($p=0.16$; Fig. 4) but females demonstrated a smaller y-intercept ($p<0.001$; Fig. 4). Relative Ct.Ar (%Ct.Ar) demonstrated no sex-specific changes with age at 30% ($p=0.12$), but females demonstrated a significantly larger y-intercept ($p<0.001$) (Fig. 4). vBMD declined with age at the same rate between sexes (30% $p=0.09$, 50% $p=0.10$) with no significant differences in y-intercept (30% $p=0.10$, Fig. 4; 50% $p=0.69$, Fig. A4).

Effects of Height on the Radius

Previous work has found height to be a significant predictor of radius bone strength [23]. Thus, height (cm) was used in this study to investigate the effects of general body size on radius morphometric parameters that would in part dictate resistance to fracture. Males in this sample were significantly taller than females ($p<0.001$). Sex-specific univariate regressions found females to be more sensitive to height differences than males (Table V). All measures of bone quantity in females showed a significant positive relationship with increasing height ($p<0.005$) with the exception of 30% %Ct.Ar ($p=0.03$) (Table V and VI). Neither robustness nor vBMD were significantly associated with height in females ($p>0.13$), however, they maintained an increasing trend with taller body height. Males demonstrated fewer morphometrics that were significantly associated with height (Table VI and AII). In males, at the 30% site, radii significantly increased in Tt.Ar ($p=0.001$, $R^2=11.2\%$), I_{ML} ($p=0.001$, $R^2=10.9\%$), and I_{AP} ($p=0.007$, $R^2=7.4\%$) with height (Table A2). However, at the 50% site in males, only Tt.Ar ($p=0.001$, $R^2=10.6\%$) and I_{ML} ($p=0.002$, $R^2=9.4\%$) increased. Figure 5 demonstrates that contrary to females, males had non-significant relationships in either Ct.Th or %Ct.Ar with height. .

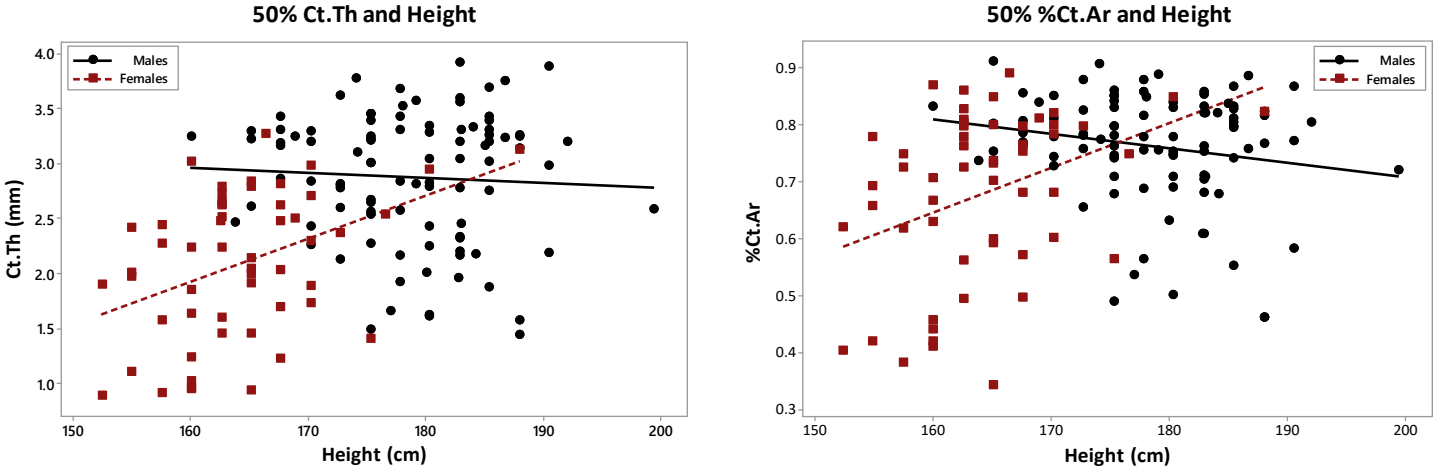

Fig. 5. Differential effects of height on Ct.Th and relative Ct.Ar (%Ct.Ar) between sexes at the 50% site. Though not significant for males (Ct.Th $p=0.61$; %Ct.Ar $p=0.07$), there is a slight decreasing trend in both morphometrics as opposed to the significant increases demonstrated by females (Ct.Th $p=0.003$, $R^2=16.1\%$; %Ct.Ar $p=0.007$, $R^2=13.1\%$;).

ANCOVA results were again performed on only parameters demonstrating statistically significant and similar directional relationships with height between sexes (Fig. 6; Table VI). No significant differences in the rate of change in Tt.Ar (30% $p=0.90$; 50% $p=0.89$) but significantly smaller y-intercepts for females (30% and 50% $p<0.001$) were found. Area moment of inertia in the medial-lateral direction (I_{ML}) also demonstrated no significant differences between rate of change (30% $p=0.71$; 50% $p=0.89$) but smaller y-intercepts for females (30% and 50% $p<0.001$). Significant relationships between I_{AP} and height for both sexes were only observed at the 30% site (Fig. A5). This parameter increased with height at the same rate ($p=0.91$), and females again demonstrated significantly smaller y-intercepts ($p<0.001$).

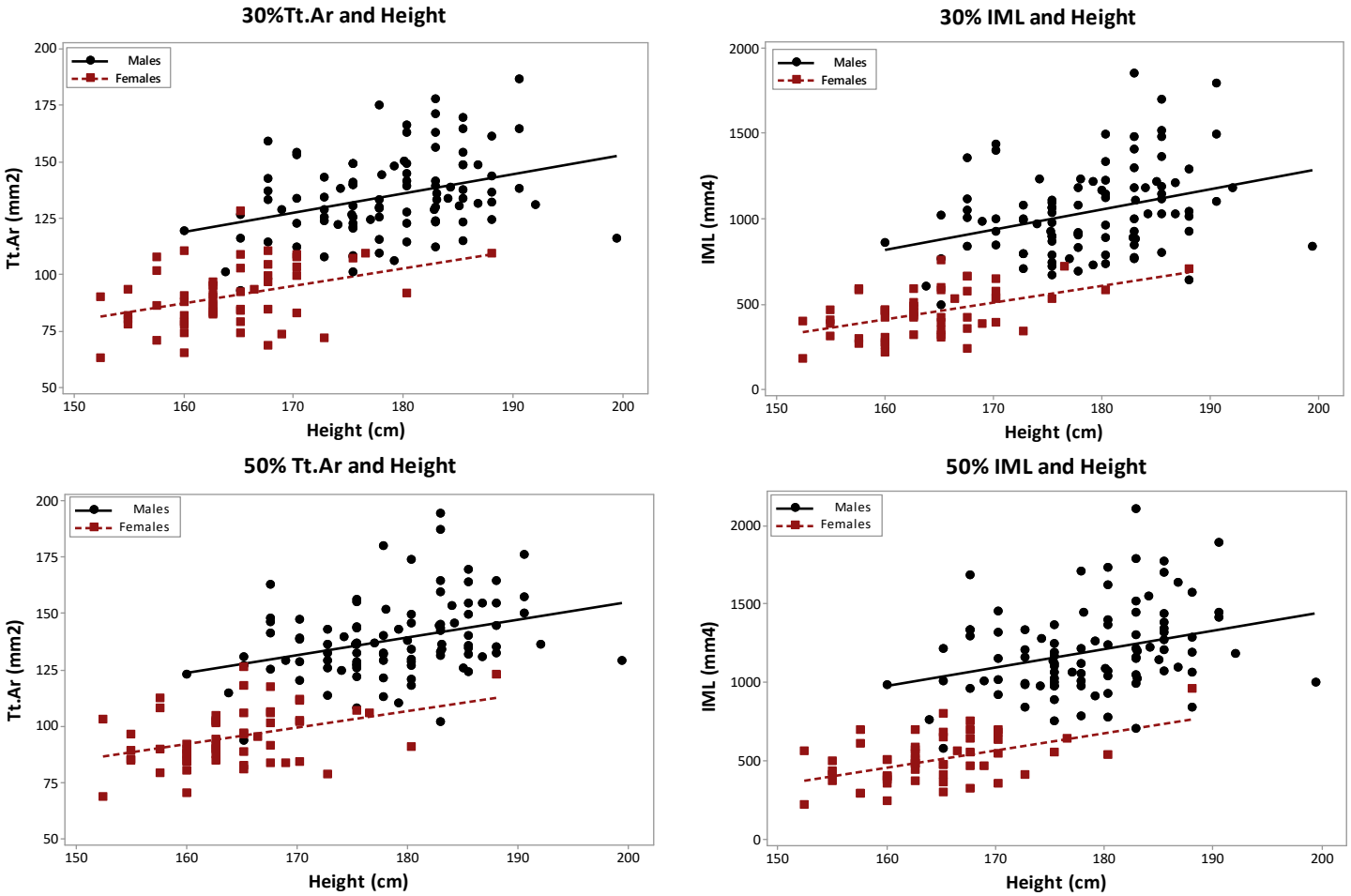

Fig. 6. Significant increases with height in both sexes were only present in Tt.Ar (females p<0.005, 30% R^2= 14.4%, 50% R^2=15.1%; males p<0.001, 30% R^2= 11.2%, 50% R^2=10.6%) and I_{ML} (females p< 0.001, 30% R^2=24.2, 50% R^2= 24.3%; males p<0.002, 30%R^2= 10.9%, 50% R^2=9.4%) for both 30% and 50% sites. ANCOVA results demonstrated that for any given height, females have a significantly smaller Tt.Ar and I_{ML} than males.

TABLE V

LINEAR REGRESSION WITH HEIGHT (CM) FEMALES ONLY

Site	Parameter	F-value (1,52)	p-value	R^2 (%)	Intercept	Slope (β)
30%	*Tt.Ar*	8.7	0.005	14.4	-36.2	0.77
	Ct.Ar	12.1	0.001	18.9	-107.9	1.01
	%Ct.Ar	5.1	0.03	9.0	-0.38	0.006
	I_{ML}	16.6	<0.001	24.2	-1175	9.9
	I_{AP}	10.5	0.002	16.8	-2040	16.8
	Ct.Th	6.9	0.01	11.7	-3.01	0.03
	robustness	1.9	0.17	3.5	0.15	0.002
	vBMD	1.8	0.18	3.4	962	0.93
50%	*Tt.Ar*	9.3	0.004	15.1	-25.1	0.73
	Ct.Ar	14.9	<0.001	22.3	-135.0	1.22
	%Ct.Ar	7.8	0.007	13.1	-0.62	0.008
	I_{ML}	16.7	<0.001	24.3	-1292	10.9
	I_{AP}	9.79	0.003	15.8	-2118	18.33
	Ct.Th	10.0	0.003	16.1	-4.33	0.039
	robustness	1.5	0.225	2.8	0.22	0.001
	vBMD	2.4	0.13	4.3	896	1.27

TABLE VI
SUMMARY SEX-SPECIFIC LINEAR REGRESSION RELATIONSHIPS* WITH HEIGHT (CM)

	30%		50%	
	Males	**Females**	**Males**	**Females**
Tt.Ar	Increase	Increase	Increase	Increase
Ct.Ar	No change	Increase	No change	Increase
%Ct.Ar	No change	No change	No change	Increase
I_{ML}	Increase	Increase	Increase	Increase
I_{AP}	Increase	Increase	No change	Increase
Ct.Th	No change	Increase	No change	No change
robustness	No change	No change	No change	No change
vBMD	No change	No change	No change	No change

*Relationship trends are reported based on statistical significance

Combined Age and Height Effects on the Radius

Due to differential relationships with height between males and females, to determine if sex-specific age-related changes were influenced by height, multivariate regressions were used. Each model included age, height, sex, and an interaction term between age*sex. When controlling for height and age, there were no longer any significant differences between male and female mean values of cortical bone morphometrics (Table VII). In these models, age was unable to predict area moment of inertia (I_{ML} or I_{AP}) values at either 30% or 50% whereas, height predicted a significant amount of variation in the cross-sectional distribution of bone measurement. Despite age explaining significant variation in all measures of bone quantity, robustness (30% site only), and vBMD when controlling for height, sex-specific effects were only observed in 50% Ct.Ar (p=0.009) and 50% %Ct.Ar (p=0.003) (Table VII). Conversely, when controlling for age, height only significantly predicted area moment of inertia (I_{ML} and I_{AP}) and Tt.Ar. These models were not optimised for fit by removing non-significant predictors due to the nature of the question investigating the combined sex-specific effects of age and height. Without optimising the models, the amount of variation explained in response variables ranged from 14.9% (50% vBMD) to 71.2% (50% I_{ML}) (Table VII).

TABLE VII
MULTIVARIATE REGRESSION MODELS

Site	**Parameter**	**p-value (age)**	**p-value (height)**	**p-value (sex)**	**p-value (age*sex)**	**R^2 adj (%)**
30%	*Tt.Ar*	0.001	<0.001	0.5	0.023	69.6
	Ct.Ar	0.004	0.028	0.24	0.073	61.3
	%Ct.Ar	<0.001	0.19	0.62	0.08	29.2
	I_{ML}	0.15	<0.001	0.32	0.06	67.2
	I_{AP}	0.12	<0.001	0.45	0.09	59.5
	Ct.Th	<0.001	0.87	0.56	0.15	42.0
	robustness	0.01	0.15	0.71	0.02	54.3
	vBMD	<0.001	0.62	0.11	0.08	18.5
50%	*Tt.Ar*	0.003	<0.001	0.25	0.06	69.9
	Ct.Ar	0.12	0.02	0.78	0.009	60.1
	%Ct.Ar	<0.001	0.46	0.10	0.003	25.9
	I_{ML}	0.03	<0.001	0.20	0.04	71.2
	I_{AP}	0.14	<0.001	0.57	0.11	54.2
	Ct.Th	<0.001	0.78	0.67	0.02	36.5
	robustness	0.02	0.31	0.42	0.04	53.8
	vBMD	<0.001	0.99	0.09	0.10	14.9

IV. DISCUSSION

The large age range represented in this sample span important biological events in bone quality such as

attainment of peak bone mass, normal aging processes, and menopause/loss of androgen hormones experienced by individuals of all body sizes. Thus, this cross-sectional study design is capable of investigating variation in the effects, across PMHS, of the subject-level variables often used to assume patterns of bone quality and injury risk on the quantity, distribution, and mineralisation of the cortex of the radius. The differential patterns between males and females in radius cortical bone response to changes in age and differences in height, further support previous findings that females are not simply smaller versions of males [15,16,18,20,26] . Similar to previous results [16] for the tibia, some of the data presented here for the non-weight bearing radius suggest sexual dimorphism in bone functional adaptation to systemic effects of age and body size represented by height. However, not all morphometric parameters in the radius demonstrated significant sex-specific relationships with these subject-level parameters. Differential biological approaches to maintaining whole bone strength between sexes could have implications for the utility of size-based only scaling techniques used to predict forearm injury, and the additional lack of sexual dimorphism in some relationships may indicate the need for alternative approaches.

Overall, females demonstrated smaller radius cortical morphometric values which aligns with previously reported data [12,27-30]. However, after controlling for total cross-sectional area (Tt.Ar), males still demonstrated significantly higher bone mass (%Ct.Ar) than females in this sample in accordance with previous work in the radius and other long bones [18,20]. This indicates male radii are not simply larger than female radii but exhibit a varying structure with overall more cortical bone within a given total area. The lack of significant differences in vBMD between sexes demonstrated in the radii included in this sample is unique. Walsh and colleagues [31] found larger cross-sectional geometry in distal male radii than female radii, as supported here, but with lower male vBMD values in pre-peak bone mass accrual individuals (16-18 years) as well as post-peak bone mass accrual (30-32 years). Dalzell et al. [27] demonstrated higher female cortical vBMD than males across a wide age range (20-79 years) in the distal radius which was not supported in this study of the diaphyseal cortical sites. The lack of significant sexual dimorphism in vBMD values at either site in the radius was also found along the length of the tibia reported by [16] using a PMHS sample that included the majority of the same individuals included in this study. Lastly, it appears there may be contradictory patterns in sex differences in vBMD in this sample dependent on age ranges. Interestingly, it appears females attained higher vBMD values around peak bone mass accrual age than males (Fig. 4 and A3), and not until older ages did most females generally fall below males in vBMD. Burghardt et al. [32] demonstrated a similar pattern through the 5th decade of life in the distal radius and distal tibia with females exhibiting higher vBMD values. This differential age-specific pattern coupled with the amount of variation and overlap between males and females in this singular parameter indicates the potential inability of vBMD, on its own, to explain the amount of variation in loading responses of the radius observed in real world scenarios.

The effects of age on cortical morphometrics indicate sex-specific and for many parameters, contradictory trends in the radius. Only males in this sample experienced significantly increasing measures of total area and robustness with age. Recent work on the midshaft radius in males with a similar age range (18-89 years), demonstrated significant increases in Ct.Ar, robustness, and I_{ML} but these relationships were dependent on whole-bone geometry [23], the influence of which was not addressed in this study and may be obfuscating trends here. Females in this sample did not demonstrate any evidence of increasing Tt.Ar (an indicator of periosteal apposition) or robustness with age, contrary to previous studies in the distal radius [28,33]. Riggs et al. [28] noted that although Tt.Ar increased in both sexes with increasing age, the concomitant decrease in Ct.Ar and Ct.Th (also demonstrated in this sample for both sexes) indicates the inability of periosteal apposition to outpace endocortical bone loss. This mechanism of compensation for age-related bone loss was observed here only in males suggesting other approaches to maintaining whole bone strength may be implemented in females, i.e., possible functional compensation whereby greater mineralisation is used to compensate for less bone quantity [34,35] and little periosteal apposition. Females in this sample demonstrated more age-related declines in bone quantity (Ct.Ar, %Ct.Ar, Ct.Th) and vBMD (Table IV) as well as larger amounts of variation explained by chronological age than in males (Table A1). The few parameters that significantly declined with age in males were Ct.Th (30% site only), relative cortical area (30% site only), and vBMD (30% and 50% sites) suggesting females may be more sensitive to bone loss with age. A lack of difference in the slopes of regression lines for the few significant parameters that declined with age in both sexes indicates that the rate of change with age did not vary between males and females in this sample as a whole. Interestingly, ANCOVA results for the y-intercept of these variables

were only smaller in females for Ct.Th (Fig.4). %Ct.Ar demonstrated significantly larger y-intercepts in females, and vBMD demonstrated no significant differences in y-intercept (Fig.4). These sex-specific patterns of change with age (Table IV) and the overall lack of variation (R^2 values ranging from 9.7-35.9%) in parameters explained by age alone (Table AI) support the assertion that simple assumptions about the ability of age to predict bone quality decline over the lifespan should be made with extreme caution when predicting fracture risk [36].

Body size in this study was assessed using height due to the non-weight bearing nature of the radius, and the previously reported significant contributions of height to predicting radius whole bone strength [23]. As shown for identical cortical morphometric parameters quantified in the tibia and their relationship with body mass [16], female radii demonstrated greater sensitivity, i.e. more significant relationships, to body size variation than males. Nearly all measures of bone quantity and distribution in female radii had a significant positive relationship with height (Table VI) though only between 11.7 and 24.3% of variation (Table V) was explained suggesting alternative influential factors are likely present. In males, only Tt.Ar and area moment of inertia (I_{ML} and I_{AP}) demonstrated positive and significant relationships with height though with only a small proportion of variation explained (Table A2). Meanwhile, neither whole-bone geometry (robustness) nor vBMD were affected by height in either sex. As robustness was normalised by total bone length (Tt.Ar/Le), the effects of height are likely removed in both sexes. Lack of relationships between body size and vBMD in the radius were not reflected in the tibia where vBMD significantly increased with body size [16] likely due to the differential functional adaptation mechanisms occurring for a weight-bearing (tibia) compared to non-weight-bearing (radius) bone. ANCOVA results for parameters that exhibited similar relationships with height between sexes (Tt.Ar and area moment of inertia) demonstrated consistent results with no significant rate of change (β) and significantly smaller y-intercepts for females. These trends were also different in the weight-bearing tibia [16] suggesting differing mechanisms mediating the effects of body size on each bone that are sex-specific and should be further explored across the skeleton. Similar to univariate effects of age reported here, the effects of height on cortical bone in the radius vary by sex (Table VI) but leave a large portion of variation unexplained in both sexes (Table V and Table AII). This may indicate that subject-level body size assumptions in predicting bone strength should be conducted with caution and in a sex-specific manner.

The multivariate regressions to investigate the combined effects of subject-level variables on radius cortical morphometric parameters in general, account for more variation in each parameter than age or height alone. However, the fit of these models, though not optimised to remove any non-significant terms, still ranged from as low as 14.9% to as high as 71.2% (Table VII). This wide range suggests that despite removing significant sexual dimorphism in parameter means when controlling for age and height of the sample, there remained a large amount of variation unexplained by these subject-level variables. A similar elimination in sex-based size differences of bone mineral density and geometric parameters when accounting for both body size and age was also noted in the femoral neck and proximal cortex by [37]. Interestingly, this was more pronounced in the older age group of 50-69 years old [37]. Both age and height were treated as continuous variables in the analyses conducted in this study which may not elucidate sex differences in means or relationships that differ between groups, i.e., young 50^{th} percentile male compared to old 5^{th} percentile female, and will be investigated in future work in this sample. Despite no significant differences in rate of change (slope) in 50% Ct.Ar and 50% %Ct.Ar in the univariate analyses, the significant interaction term (age*sex) indicates that although there was no longer any significant sexual dimorphism (in means) when controlling for age and body size, the effects of age on these parameters differed between males and females even after differences in height were removed. Interestingly, after accounting for body size, age was still able to predict vBMD but the R^2 values were the lowest of any morphometric parameter suggesting assumptions about this parameter across individuals of varying ages and body sizes should be made with caution. These results require more investigation to elucidate more nuanced relationships across the age spectrum and throughout body size categories; however, the large amount of unexplained variation in these data may support previous work that found inaccuracies when scaling across or even within sexes based upon size [15].

Additionally, much like considering the combined effects of subject-level variables, to truly understand sex differences in bone quality that would drive differential response to loading, a combination of these morphometric parameters should be considered. Investigating measures of bone quantity, distribution, and mineralisation in isolation from each other is an important initial step to quantifying variation across individuals of varying ages and body sizes; however, this approach does not account for the ability of bone to functionally

compensate or coordinate traits to maintain strength [19,20]. Jepsen and colleagues suggest the covariance between robustness, cortical area, and vBMD are the minimum necessary traits to assess differences in male and female whole bone function [18,38]. The response of *slender* or *narrow* bones to changes in age and body size vary compared to *robust* or *wide* bones [23,39] and may be sex-specific which will be investigated in future work. These effects of categorizing the radius by whole-bone geometry to investigate differences in age or body size changes may provide an alternative approach beyond simply using sex based assumptions to understand bone strength. Lastly, the biological relevance and implications of these complex relationships between subject-level variables and cortical morphometrics of the radius will be quantified in future work using dynamic experimental testing in multiple realistic loading scenarios.

The limitations of this study include its cross-sectional nature in that the PMHS radius represents the product of adaptation to systemic, environmental, and mechanical environments of each individual's lifetime, but does not represent longitudinal changes in cortical bone morphometric parameters. This approach does allow the investigation of subject-level demographics (age and body size) between sexes across the sample and captures variation in these parameters between PMHS. Specific behavioral activities or preferences, including handedness, is unknown for this sample and likely affected the development, maintenance, and loss of bone in the radius for each PMHS. However, this study includes a large sample size of individuals of varying ages, body sizes, and behavioral preferences that represent individuals in the modern US population in need of safety mechanisms to mitigate forearm injury. Lastly, the biological relevance of these sex-specific (or lack thereof in some cases) relationships presented here is unknown but will be elucidated in future work including dynamic experimental testing of these radii.

V. CONCLUSIONS

This study quantifies variation in radius cortical bone morphometric parameters for a sample that represents a wide range of ages and body sizes. Although cross-sectional in nature, exploring the sex-specific effects of age and height on these parameters is an important step to understanding the variation in loading responses observed in real world injury scenarios. Female radii are significantly smaller than male radii as expected, yet even after normalising for gross size, females demonstrated significantly less cortical bone (%Ct.Ar) than males suggesting a fundamental difference in bone structure. Changes in morphometric parameters with age and body size were not identical between the sexes with varying amounts of significant relationships with these subject-level variables. Multivariate regressions indicated that controlling for age and height removes any sexual dimorphism in individual parameter means potentially indicating a lack of need for scaling females as smaller versions of males. However, when investigating the effects of age on %Ct.Ar after controlling for height, the rate of change was significantly different in males compared to females indicating sex-mediated age-related bone loss. The fundamental differences in bone functional adaptation between males and females, and the continued support of the emerging body of evidence that females are not simply smaller versions of males but have different cross-sectional morphometric properties, suggests size-based scaling techniques may not be appropriate or necessary in predicting skeletal injury risk. More work is necessary to explain the differential response to loading between sexes in the radius.

VI. ACKNOWLEDGEMENTS

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VII. REFERENCES

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VIII. APPENDIX

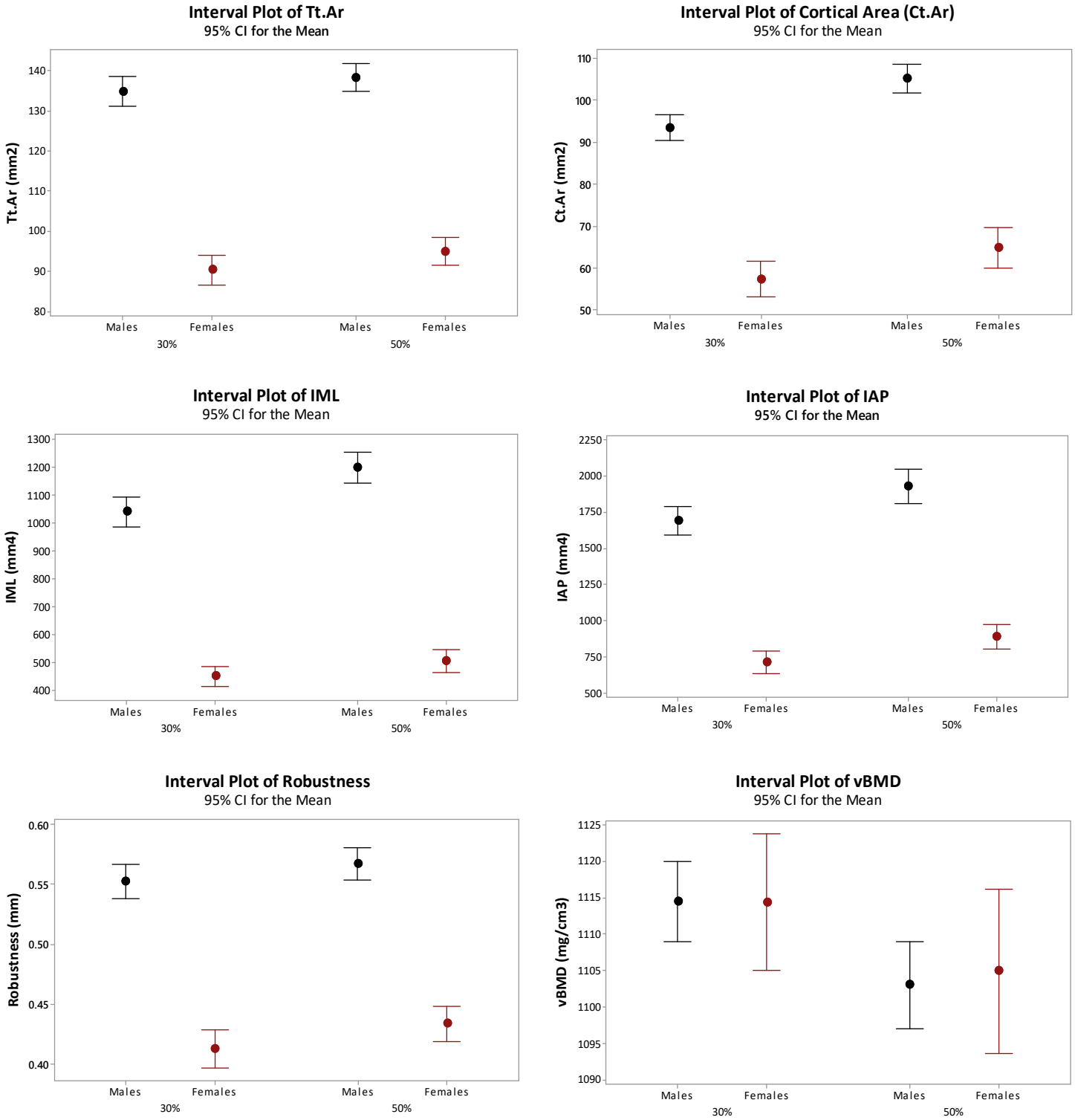

Fig. A1. Interval plots demonstrating significant ($p<0.003$) sex differences in Tt.Ar, robustness, and I_{ML} at both sites. No significant differences in vBMD existed between sexes ($p>0.81$).

TABLE AI
LINEAR REGRESSION WITH AGE (YRS)

Site	Parameter	Sex	F	p-value	R^2 (%)	Intercept	Slope (β)
30%	*Tt.Ar (mm^2)*	Male	12.0	0.001	11.3	106.6	0.44
		Female	0.2	0.63	0.4	93.8	-0.053
	Ct.Ar (mm^2)	Male	0.9	0.35	0.9	100.0	-0.10
		Female	15.3	<0.001	22.7	85.4	-0.44
	%Ct.Ar	Male	18.8	<0.001	16.7	0.88	-0.003
		Female	24.8	<0.001	32.3	0.93	-0.005
	I_{ML} (mm^4)	Male	3.3	0.07	3.4	820	3.47
		Female	5.0	0.03	8.8	602.4	-2.37
	I_{AP} (mm^4)	Male	3.5	0.06	3.6	1263	6.73
		Female	2.3	0.14	4.2	929	-3.34
	Ct.Th (mm)	Male	14.3	<0.001	13.2	3.5	-0.01
		Female	27.9	<0.001	34.9	3.2	-0.02
	robustness (mm)	Male	12.2	0.001	11.5	0.44	0.001
		Female	0.03	0.87	0.1	0.42	-0.00
	vBMD (mg/cm^3)	Male	10.9	0.001	10.4	1154.6	-0.63
		Female	24.5	<0.001	32.0	1186.9	-1.13
50%	*Tt.Ar (mm^2)*	Male	8.9	0.004	8.7	114.8	0.37
		Female	0.2	0.68	0.32	97.7	-0.042
	Ct.Ar (mm^2)	Male	0.4	0.54	0.4	100.2	0.08
		Female	13.0	0.001	20.0	94.1	-0.46
	%Ct.Ar	Male	3.8	0.05	3.9	0.85	-0.001
		Female	23.3	<0.001	30.9	0.99	-0.005
	I_{ML} (mm^4)	Male	5.6	0.02	5.6	898	4.72
		Female	2.2	0.14	4.1	618.8	-1.77
	I_{AP} (mm^4)	Male	5.2	0.03	5.2	1452	1.75
		Female	2.3	0.14	4.1	1129	-3.71
	Ct.Th (mm)	Male	2.5	0.11	2.6	3.32	-0.007
		Female	24.4	<0.001	32.0	3.48	-0.022
	robustness (mm)	Male	9.2	0.003	8.9	0.48	0.0014
		Female	0	0.95	0.01	0.44	-0.00
	vBMD (mg/cm^3)	Male	9.1	0.003	8.8	1143.5	-0.63
		Female	17.1	<0.001	24.8	1182.0	-1.204

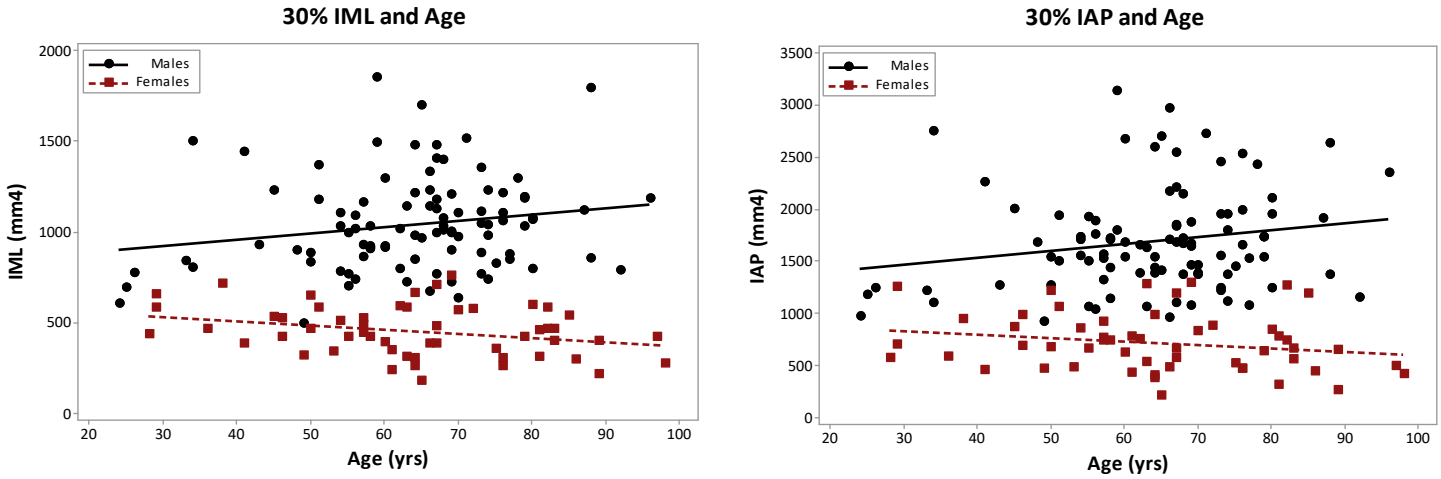

Fig. A2. Univariate regressions of I with age at the 30% site for males and females.

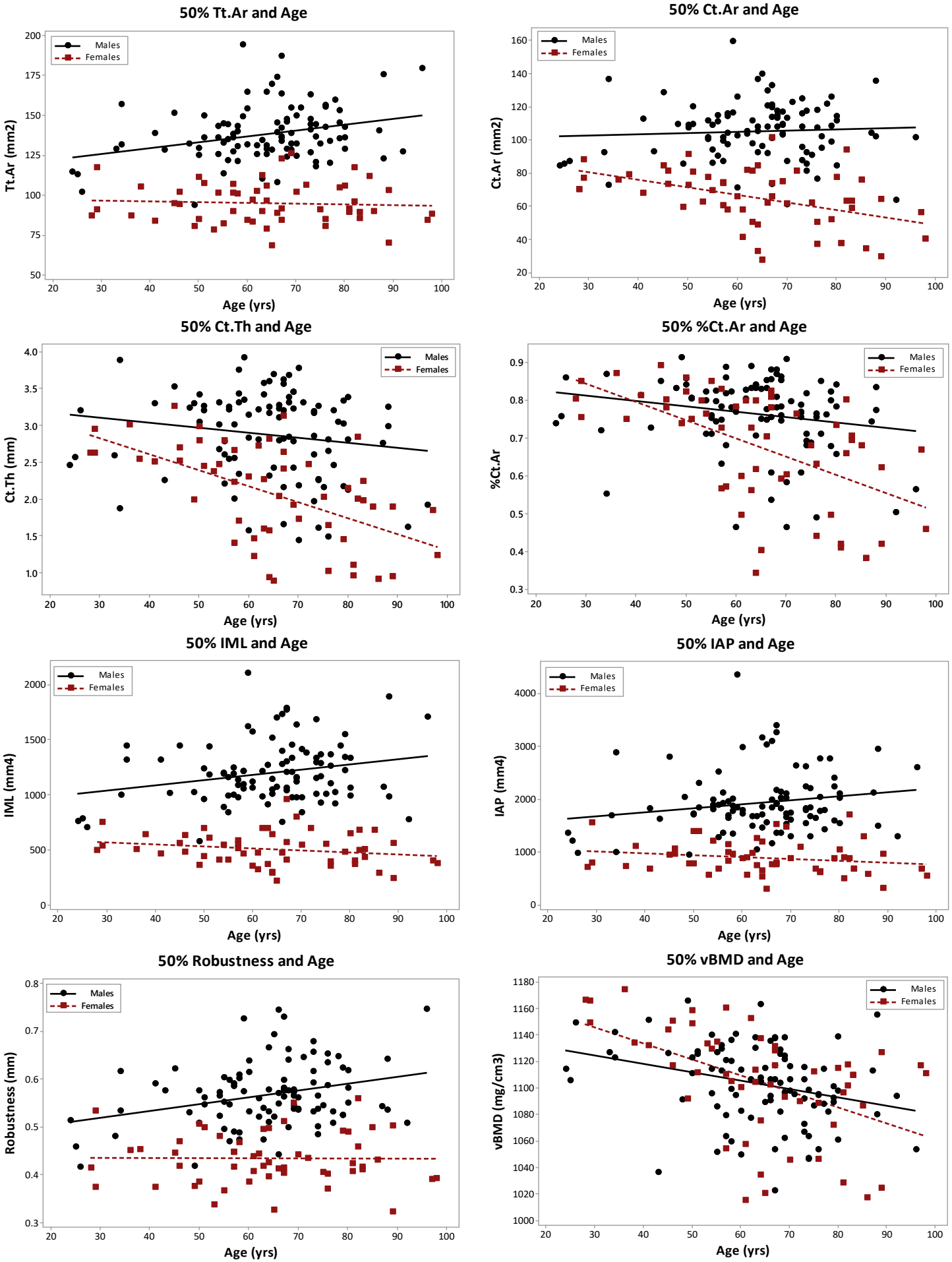

Fig. A3. Univariate linear regressions of all morphometrics with age at 50% site for males and females.

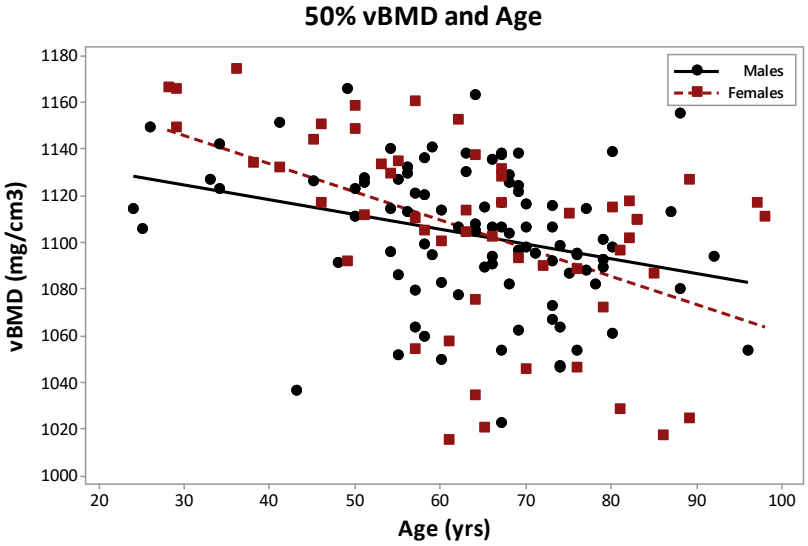

Fig. A4. ANCOVA results for change in vBMD with age at 50% site between males and females.

TABLE AII
LINEAR REGRESSION WITH HEIGHT (CM) MALES ONLY

Site	Parameter	F-value (1,94)	p-value	R^2 (%)	Intercept	Slope (β)
30%	*Tt.Ar*	11.8	0.001	11.2	-15.8	0.84
	Ct.Ar	1.8	0.19	1.9	43.8	0.28
	%Ct.Ar	3.2	0.08	3.3	1.14	-0.002
	I_{ML}	11.5	0.001	10.9	-1077	11.9
	I_{AP}	7.5	0.007	7.4	-1523	18.0
	Ct.Th	0.3	0.60	0.3	3.29	-0.004
	robustness	0.3	0.57	0.3	0.45	0.0001
	vBMD	0.0	0.96	0.0	1117.9	-0.02
50%	*Tt.Ar*	11.2	0.001	10.6	-1.4	0.78
	Ct.Ar	1.3	0.26	1.4	56.1	0.28
	%Ct.Ar	3.5	0.07	3.6	1.22	-0.003
	I_{ML}	9.8	0.002	9.4	-899	11.74
	I_{AP}	6.0	0.02	5.9	-1803	20.91
	Ct.Th	0.3	0.61	0.3	3.66	-0.004
	robustness	0.05	0.82	0.05	0.53	0.0002
	vBMD	0.03	0.85	0.04	1089.1	0.078

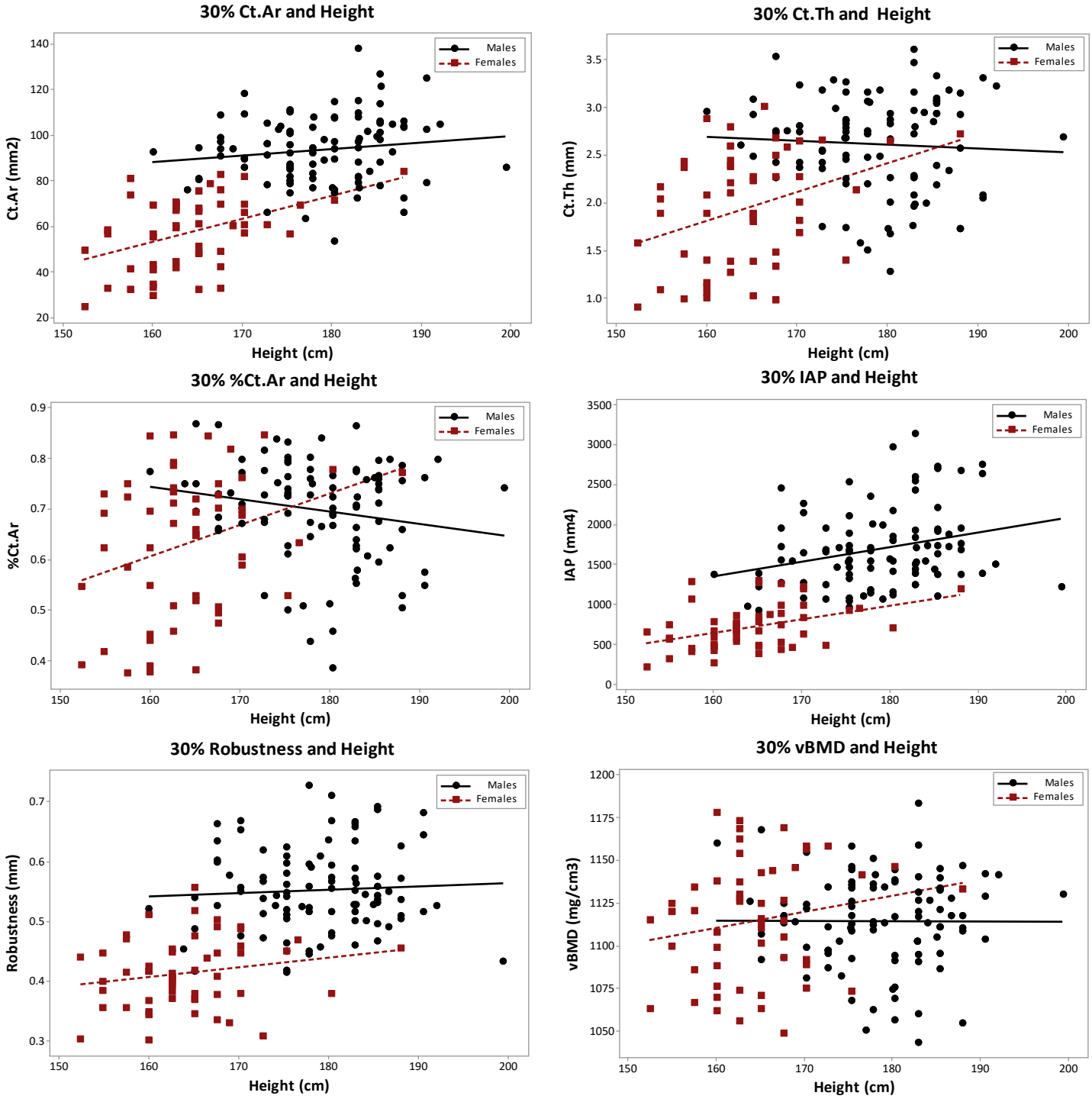

Fig. A5. Univariate regressions of Ct.Ar, Ct.Th, Ct.Ar, I_{AP}, robustness, and vBMD with height for 30% site for males and females.

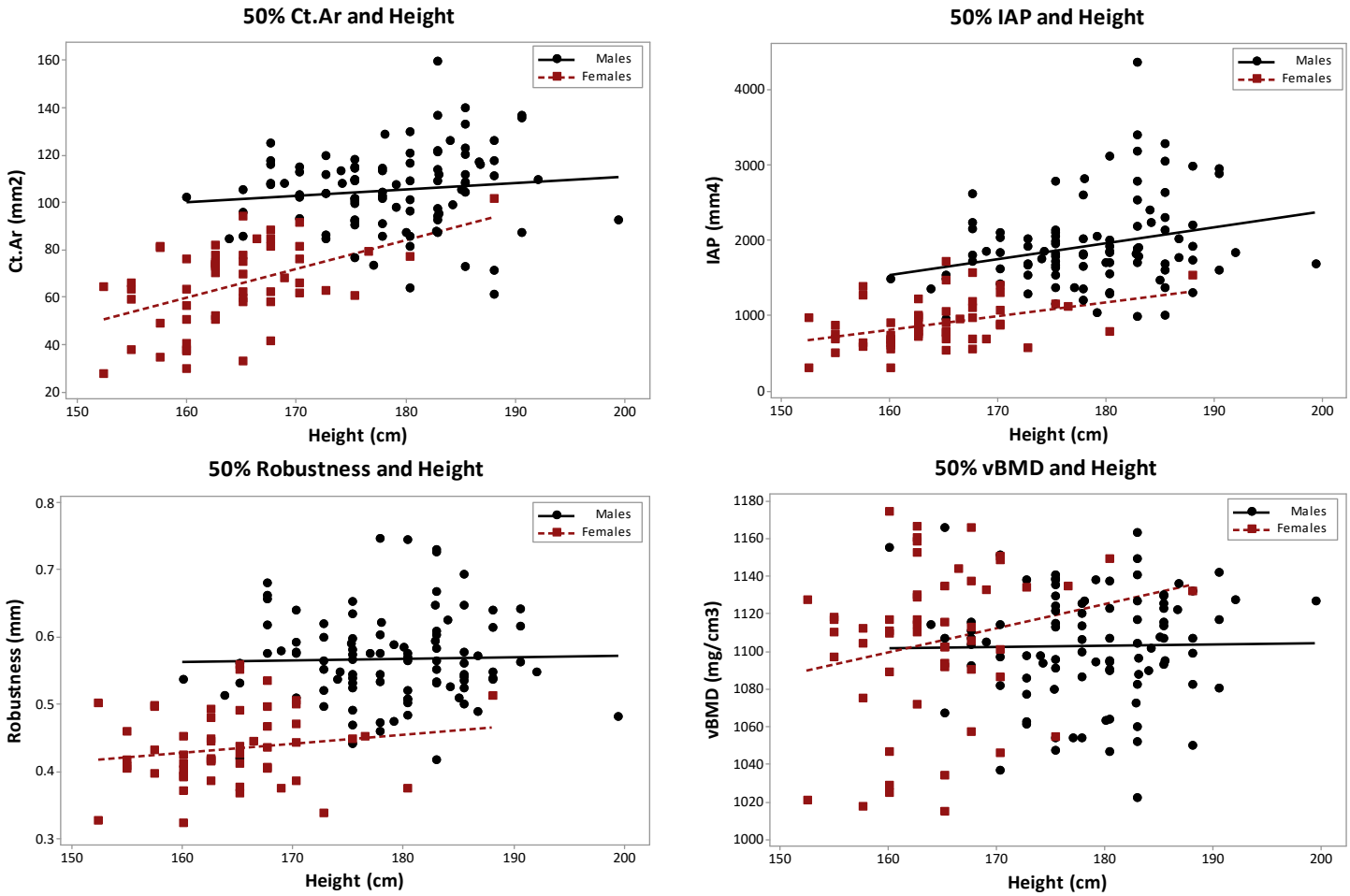

Fig. A6. Univariate regressions of Ct.Ar, I_{AP}, robustness, and vBMD with height for 50% site for males and females.