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1 **Histomorphometry and cortical robusticity of the adult human femur**

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11 **ABSTRACT**

12 Recent quantitative analyses of **human** bone microanatomy, as well as theoretical models
13 that propose **bone micro- and gross anatomical** associations, have started to reveal **insights**
14 **into** biological links that **may** facilitate remodeling **processes**. **However**, relationships between
15 bone **size** and the underlying cortical bone histology remain largely unexplored. The goal of
16 this study is to determine the extent to which static indicators of bone remodeling **and**
17 **vascularity**, measured using **histomorphometric** techniques, relate to femoral midshaft
18 cortical width and robusticity. Using previously published and new quantitative data from 450
19 adult human male (n = 233) and female (n = 217) femora, we determine if these aspects of
20 femoral size relate to bone microanatomy. Scaling relationships are explored and interpreted
21 within a context of tissue form and function. Analyses revealed that the area and diameter
22 of Haversian canals and secondary osteons, and densities of secondary osteons and osteocyte
23 lacunae from the sub-periosteal region of the posterior midshaft femur cortex were
24 significantly, but not consistently, associated with femoral size. Cortical width and bone
25 robusticity were correlated with osteocyte lacunae density and scaled with positive allometry.
26 Diameter and area of osteons and Haversian canals decreased as the width of cortex and bone
27 robusticity increased, revealing a negative allometric relationship. **These results indicate that**
28 **measures of cortical** bone remodeling **and vascularity products** link to **femur** size. Allometric
29 relationships between more robust human femora with thicker cortical bone and histological
30 products of bone remodeling correspond with principles of bone functional adaptation.
31 **Future studies may** benefit from combining **bone** histomorphometric data with
32 measurements of **bone** macrostructure.

33

34 **Keywords:** **bone** histomorphometry, osteocyte lacunae, osteons, Haversian canals, femur,
35 **cortical bone, bone functional adaptation**

36 **Abbreviations:** Cortical width (Ct.Wi), Cortical width robusticity index (Ct.Wi.RI), intact
37 osteon density (N.On), fragmentary osteon density (N.On.Fg), osteon population density
38 (OPD), osteon area (On.Ar), Haversian canal area (H.Ar) and diameter (H.Dm), osteocyte
39 lacunae density (Ot.Dn), reduced major axis regression (RMA)

40

41 INTRODUCTION

42 Analyses of bone microstructure can offer insights into skeletal growth, metabolism and
43 structure-function adaptive relationships [1-3]. More specifically, histomorphometric
44 examination yields remodeling data that can be evaluated in relation to mechanical loading
45 history, diet, and disease [e.g. 4-7], and has been of particular importance in studies
46 investigating the relationship between ontogeny, age-related disease, and bone modeling
47 and remodeling [e.g. 8-10]. Recently, one of us [2] reported significant positive and negative
48 correlations between different static histomorphometry variables that relate to bone
49 remodeling associated with mechanical stimuli. Yet, relationships between bone gross
50 anatomy and the underlying bone microstructure remain largely unexplored. Therefore, the
51 present study builds upon this previous work, and examines midshaft femur size against
52 histomorphometric data [2]. Our goal is to investigate the extent to which static
53 histomorphometric evidence of cortical bone remodeling and vascularity relates to midshaft
54 cortical width (Ct.Wi)¹, and a femoral robusticity index (Ct.Wi.RI) calculated from Ct.Wi data.
55 We aim to provide insights into the complex relationship between outer and inner bone
56 anatomy in relation to biological (metabolic and functional) processes. The modern human
57 sample in our study is unique, deriving from a large well preserved recent archaeological
58 skeletal collection curated at the University of Kent (UK). Usually, except for diagnostic bone
59 biopsies taken from patients [e.g. 12], research into cortical histomorphometric variation in
60 humans relies on smaller samples of cadavers [e.g. 5-7], or comparative experimental studies
61 utilising non-human animal models [e.g. 8]. In addition to revealing the relationship between
62 the size of a femur and the underlying products of bone remodeling, the present study
63 extends previously reported human cortical histomorphometric data and findings [2].

64 ¹For the sake of clarity, and to ensure that our study follows standard histomorphometry
65 nomenclature [11], we refer to the cortical distance between the endosteum and
66 periosteum as “cortical width” (defining transverse 2D measurements of diaphyseal
67 cortex) rather than “cortical thickness” (implying 3D measurements) [e.g. 24].

68

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70

71

72 **Form and function of limb long bones**

73 The biomechanical properties of lower limb long bone diaphysis are best explained using basic
74 structural engineering principles [13-14]. Large mechanical stress sustained by the human leg
75 will be accommodated by periosteal expansion, strengthening bone tissue and minimising
76 fracture risk [15]. Previous experimental studies have demonstrated bone enlargement under
77 dynamic and/or repetitive mechanical loading regimes, and a decline in bone mass when load
78 bearing is removed [e.g. 16-17]. Based upon these types of correlations, cross-sectional
79 thickness or width of the cortex, robusticity index, measures of area moments of inertia, or
80 simple cross-sectional geometry, have all served as proxies for the functional adaptation of
81 the human femur [see 18 for evaluation].

82 At the histological level, when examined in a transverse plane, products of cortical remodeling
83 may be informative of functional adaptation [e.g. 1-3, 7]. These include geometric properties
84 (e.g. surface area, diameter, shape circularity) of secondary osteons (hereafter “osteons”) and
85 Haversian canals (indicative of bone vascularity), as well as densities of osteons and osteocyte
86 lacunae [19]. By summing the number of fragmentary and intact osteons, a total osteon
87 population density can be estimated for an examined section area, indicating an average
88 number of bone remodeling products, serving as a proxy for bone density [2, 19]. Similarly,
89 osteocytes (in living bone), or osteocyte lacunae (in preserved ancient bone) can be totalled
90 per section area to indicate average density and, by extension, reflect an approximate rate of
91 osteocyte proliferation [2, 20]. These variables may then be linked to bone functional
92 adaptation given the mechanosensing properties of osteocytes [21]. Relatively smaller or
93 larger osteon and Haversian canal area and diameter measurements represent transverse
94 cross-sectional surfaces of bone microstructure, and may indicate how fast or slowly, and/or
95 frequently cortical bone is filled by Basic Multicellular Units (BMUs) [22]. Indeed, previous
96 human and non-human animal research demonstrated higher osteon and osteocyte lacunae
97 densities, and smaller osteons and Haversian canals at bone sites associated with larger strain,
98 mechanical stress, or type (direction) of mechanical load [e.g. 22-28].

99 Given that modeling of the human skeleton ceases almost completely with the onset of
100 adulthood, information about the underlying remodeling activity can be mainly accessed
101 using microscopic methods. Although it is estimated that only an approximate 30% of overall

102 remodeling activity relates to micro-damage repair [29], the accumulation of bone remodeled
103 in response to function should manifest differently when evaluating the same bone type, of
104 different sizes. However, limited empirical research has been undertaken investigating direct
105 bone macro- and microscopic scaling relationships in human bone. Recent mathematical
106 theoretical models of remodeling demonstrated that mean biomechanical stress
107 nonuniformity has an important role in trabecular bone functional adaptation [30].
108 Experimentally, initial links have been identified between bone robusticity and cortical
109 remodeling, warranting further investigation [31-34]. For example, using multiple methods
110 applied to ten human cadaveric tibiae, Goldman et al [31] showed that bone robusticity had
111 an effect on cortical remodeling by increasing the numbers and size of osteons. It was
112 suggested that remodeling may be subject to global signalling that influences bone
113 robusticity. Another recent study [32] demonstrated that differences in bone mass
114 attainment due to sexual dimorphism may not be entirely representative of the classic
115 perception that females attain more slender bones than males. Using a large sample (n = 241)
116 of femora derived from an anthropological skeletal collection, Jepsen et al. [32] showed that,
117 in fact, bone mass is relative to sex-specific body and bone size. This is supported by an earlier
118 study suggesting similar bone mechanical properties for different bone size in males and
119 females [33]. Finally, using 115 adult human long bones, Schlecht and Jepsen [34] indicated a
120 co-variance between bone robusticity and strength/stiffness, highlighting that meaningful
121 analyses of skeletal traits may be best achieved when multiple aspects of bone functional
122 adaptation (e.g. size, volume, stiffness) are considered together. Therefore, these studies
123 have begun to indicate clear relationships between bone microanatomy and gross
124 morphology. Recently, we [2] reported a series of positive and negative correlations between
125 classic static histomorphometry variables representing products of cortical remodeling in the
126 human midshaft femur. Here, these data are analysed in relation to femoral cortical width
127 and its associated femoral robusticity in the same sample, extending the original findings. Two
128 “themes” are investigated, exploring scaling relationships of bone metabolic and structural
129 change:

130 Predictions:

- 131 a) Functional relationships - if femoral diaphyseal cortical properties are influenced
132 and/or underlie mechanically induced remodeling, the following basic engineering

133 principles apply: (i) osteon and osteocyte lacunae densities should correlate with an
134 increase in cortical width and femoral robusticity and scale with positive allometry,
135 but (ii) osteon and Haversian canal size and diameter should correlate with an increase
136 in cortical width and femoral robusticity and scale with negative allometry.

137 b) Dimensional relationships – if bone microstructure is a simple reflection of the intra-
138 specific variation in femur size (i.e. “naturally” larger vs. “naturally” smaller bone),
139 then all histology variables should increase in size or density at proportionally the
140 same rate as cortical width and femoral robusticity increase in size. Under this
141 scenario, the growth ratio between the variables will be isometric.

142

143 **MATERIALS AND METHODS**

144

145 Data used in our study derive from a skeletal sample (n = 450) of British modern human adult
146 remains curated in the Skeletal Biology Research Centre at the University of Kent (UK). These
147 remains were recovered from one site and have been dated to between 900 to 400 years ago
148 [24]. Examination of this skeletal material followed standard permissions and anthropological
149 codes of practice and ethics². Given the historical context of this sample, Human Tissue Act(s)
150 regulations do not pertain to our study.

151 **Individuation procedures**

152 Standard anthropological methods of age-at-death and sex estimation were followed to
153 reconstruct the biological profile of each adult [35]. A total of 450 adults was separated into
154 age and sex sub-groups, resulting in: 217 females, 233 males, 126 young (20 – 35 years old)
155 and 319 middle-aged adults (35 – 50 years old), and 5 old adults (50+ years old) (four males,
156 and one female).

157 ²Code of Ethics of the American Association of Physical Anthropologists (2003)
158 <http://physanth.org/documents/3/ethics.pdf>, British Association for Biological Anthropology
159 and Osteoarchaeology Code of Practice (2010) [http://www.babao.org.uk/index/ethics-and-](http://www.babao.org.uk/index/ethics-and-standards)
160 [standards](http://www.babao.org.uk/index/ethics-and-standards), Mays S, Elders J, Humphrey L, White W, and Marshall P (2013) Science and the
161 Dead: guidelines for the destructive sampling of archaeological human remains for scientific
162 analysis. Advisory Panel on the Archaeology of Burials in England. English Heritage.

163 Further sub-divisions were made into 49 young males and 77 young females, 139 middle-aged
164 females, and 180 middle-aged males (Table 1). Due to the small sample size, individuals in the

165 “old” age category (aged 50 or more years) were excluded from analyses that controlled for
166 age.

167 **Macroscopic and microscopic femoral examination**

168 The process of femoral midshaft sectioning, and thin section preparation in this sample has
169 been previously described elsewhere [e.g. 2, 24]. The thin sections were originally produced
170 as part of a larger project [36]. In brief, right (n = 367) and left (n = 83) femora, selected from
171 individuals with no evident skeletal pathology, were pooled due to a lack of data asymmetry.
172 In order for the sectioning to be as minimally invasive as possible, the posterior quarter of
173 midshaft diaphysis was extracted (approximately 1 ± 0.2 cm thick) and examined. The
174 posterior femoral aspect was also chosen as a suitable sectioning location as it relates closely
175 to lower limb behaviour (i.e. the sectioning location overlaps linea aspera). Prior to thin
176 section preparation, Ct.Wi was recorded using standard digital calipers by placing the
177 measuring needles on the most external surfaces of the endosteum and periosteum.
178 Robusticity indices were calculated by dividing Ct.Wi data by maximum femoral length [18].
179 Thin section preparation followed standard procedures [see 2]. Samples were embedded in
180 Buehler EpoxiCure[®] resin, cut on a precision saw, attached to microscope slides, ground and
181 polished to reveal histology. This was followed by cleaning and dehydrating in a series of
182 ethanol baths and covering with glass slips.

183 Some of the histology data examined here were previously analysed in other studies
184 addressing questions that are not the focus of the present research [e.g. 2, 24, 37]. However,
185 relationships between histomorphometric variables and femoral cortical width and
186 robusticity are examined here for the first time. In brief, values of intact (N.On), fragmentary
187 (N.On.Fg), and total osteon population density (OPD), as well as osteon area (On.Ar),
188 Haversian canal area (H.Ar) and diameter (H.Dm), and osteocyte lacunae density (Ot.Dn) were
189 recorded under a BX51 Olympus microscope with an Olympus DP25 camera. Additional
190 imaging of thin sections (Figure 1) was undertaken using AmScope MU130 microscope digital
191 camera and its associated AmScope (2016) software. A mean value was calculated for each
192 variable from a maximum of six regions of interest (ROIs), extending along the sub-periosteal
193 cortical region. Measurements and counts were performed in CELL[®] Live Biology Imaging
194 software (Olympus). In some cases, the archaeological condition of samples meant it was

195 difficult to consistently select the exact same ROIs (e.g. due to localised bioerosion). However,
196 **data are** in line with current **standards** (recommending 25 – 50 osteons to be evaluated per
197 section), **and were captured** using a range of 2X, 4X, 10X, 20X, and 40X magnification [2].

198 **Inferential statistics**

199 Statistical analyses were undertaken using IBM SPSS Statistics 22.0® (2013), R (2.5.0, i386
200 3.4.0)® (2007), and Past3® [38]. Data were examined for: normal distribution (Kolmogorov-
201 Smirnov or Shapiro Wilk tests depending on sample size within age and sex groupings), intra-
202 observer error (n = 45), and data asymmetry between right and left **femora** (independent
203 samples t-test) [36]. The macro-microscopic associations were investigated in two stages.
204 Simple correlations were performed first, Reduced Major Axis (RMA) regressions were
205 undertaken second. In both stages, cortical width, and robusticity indices, were considered
206 independent variables and thus plotted on the x axis. This is because our research questions
207 centre on determining the extent to which histology (y axis) depends on macrostructure.
208 However, it is noted that a RMA regression does not require a well defined mutual
209 relationship between the two variables [39]. In fact, it is acceptable to use RMA in tests which
210 include somewhat arbitrary, but co-dependent x and y variable interaction [39]. This is a
211 suitable approach in the present study, given there may never be absolute certainty as to
212 whether, universally, bone robusticity influences histology, or histology determines bone
213 robusticity.

214 Firstly, due to skewed raw data, the simple correlations were sought using non-parametric
215 Spearman's tests in the entire sample, and then repeated within each of the age and sex sub-
216 groups. The strength of each correlation was evaluated by the value of r^2 (coefficient of
217 determination) with coefficients equal to or larger than 20% - 40% being deemed weak to
218 moderate correlations [40]. Here, scattergrams for the three strongest correlations are
219 presented (Figures 2-3), and results are interpreted only for r^2 values equal to higher than
220 20%. All results are presented in tables (Tables 2-5; Supplement Tables 2-3). A line of best fit
221 is included in the Scattergrams (Figures 2-3) to visualise the direction in data change. Given
222 the skewness of raw data, we also fitted each plot with a loess line to illustrate monotonic
223 downward or upward trend(s) in data [41]. As previously documented [2, 24], no intra-
224 observer error was identified, but there were inconsistent patterns in histology data

225 distribution (i.e. fluctuating between normal and abnormal within age and sex sub-groups),
226 and though transformed for the purpose of parametric testing in our previous studies [e.g. 2,
227 24], raw data were analysed here via non-parametric tests. This was necessary because of the
228 new addition of macroscopic cortical width measurements, and flexibility in making no
229 assumptions about the underlying data distribution in the broader (or interpretive) context
230 of bone metabolism. The correlations were performed on every single histology variable,
231 along with additional four histology “ratio” variables (presented in the Supplement):

- 232 • H.Ar: On.Ar - indicating how much of lamellar wall per osteon there is per section,
233 along with any mutual, accompanying changes in the size of Haversian canal and
234 osteon surface area (the higher the ratio value, the larger the microstructural unit,
235 and the thinner the lamellar portion of osteons);
- 236 • N.On: OPD - indicating a biological correspondence of intact osteons to total osteon
237 population (the higher the value, the denser the bone section in unremodeled
238 osteons);
- 239 • Ot.Dn: OPD – indicating a biological correspondence of osteocyte lacunae to total
240 osteon population (the higher the value, the denser the bone section);
- 241 • Ot.Dn: On.Ar – indicating a biological correspondence of osteocyte lacunae to osteon
242 surface area (a value of 1 would suggest a tight relationship between osteon size and
243 cell density, and thus disprove the hypothesized opposite effect of biomechanical
244 stimulation upon cortical histomorphometry).

245 Secondly, regression of log-transformed data were conducted through RMA analysis to
246 examine the growth ratio between the variables. This statistical model accounts for variation
247 in data plotted on both the x and y axis (given these are data from deceased humans, and
248 bone remodeling rates vary intra-specifically) [39, 42]. Additionally, the RMA regression is
249 symmetrical, whereby deviations in x and y data are minimized [38]. Macrostructure data on
250 the x axis were regressed against histology (and ratio) data on the y axis. The RMA regression
251 results were evaluated based on slope (b), r^2 (coefficient of determination), the 95% slope
252 confidence interval (95% CI), intercept, and significance (p) values. Scattergrams representing
253 the three strongest RMA regression results are presented (Figures 2-3), and all results are
254 reported in Tables 4-5 (along with Supplement Table 3). The RMA regressions were only
255 undertaken on the strongest initial correlations identified in the first step of the analysis

256 (Tables 2-3, Supplement Table 2). Isometric macro-microscopic growth is identified when/if b
257 equals 1. This means that the growth ratio between femoral size and the underlying
258 microscopic structures is constant, indicating a dimensional anatomical effect. Negative or
259 positive allometry is identified when/if b is < 1 , or > 1 respectively, which is also evaluated
260 through the 95% CI's. This means that the growth ratio between femoral size and the
261 underlying microscopic structures is not constant, and one increases at a proportionally
262 faster/slower rate than the other. When viewed alongside our predictions, this indicates a
263 bone functional adaptation effect.

264 **RESULTS**

265 Descriptive statistics for histology data were previously published in [2] and partly in [23, 37].
266 Descriptive data for the new Ct.Wi and Ct.Wi.RI variables are given in Table 1, whereas
267 histology ratio data appear in the Supplement Table 1. Results from the inferential analysis
268 are presented in Tables 2-5, and Supplement Tables 2-3. Out of 198 correlation tests
269 performed, 145 (~73%) were statistically significant at $p < .05$ (Tables 2-3, Supplement Table
270 2). Using Ct.Wi data only (99 tests), 70 (~71%) were statistically significant (p range from 0.000
271 to 0.048) (Table 2, Supplement Table 2, Figures 2-3). Twelve of those were of moderate
272 strength (r range from -0.596 to -0.432). Further 29 significant correlations were weak,
273 explaining more than 10% but less than 20% of data variation. The remaining significant
274 results failed to explain substantial portions of data ($< 10\%$), though some general trends in
275 data were still identified.

276
277 Subsequent analyses, where femoral robusticity calculated from Ct.Wi was assessed against
278 the histology variables (repeated 99 tests), revealed 75 (~76%) statistically significant (p range
279 from 0.000 to 0.046) correlations (Table 3, Supplement Table 2, Figure 3). Seven of which
280 were also of moderate strength (r range from -0.517 to 0.424). There were 34 weak significant
281 correlations (explaining $> 10\%$ but $< 20\%$ of data variation), and the remaining significant
282 correlations failed to explain $> 10\%$ of data variation. Therefore, there was a slight
283 improvement in the number and strength of the relationships between Ct.Wi.RI, and the
284 histomorphometric variables (Table 3; Supplement Table 2, Figure 3).

285

286 Reduced Major Axis regression analyses revealed consistent relationships between femoral
287 cortical width and the size of the histology variables. The relationship of Haversian canal size
288 (area and diameter), and the relationship of osteon area, to cortical width is negatively
289 allometric (Tables 4-5; Figures 2-3; Supplement Tables 1-3). Thus, individuals with smaller
290 Haversian canals, and smaller osteons, have a relatively greater cortical width, compared to
291 individuals with thinner femoral cortical bone. The scaling relationship between our measure
292 of femoral size and the histology frequency and density variables is less consistent. The
293 relationship of intact osteon density and osteon population density to cortical width is
294 isometric, while osteocyte lacunae density and cortical width scale with positive allometry.
295 This implies that the frequency of osteons and cortical width increase or decrease in number
296 or size at relatively equivalent rates. In contrast, individuals with fewer osteocyte lacunae
297 have relatively thinner femoral cortical bone, but individuals with thicker femoral cortices
298 have a proportional greater density of osteocyte lacunae. This latter pattern occurs because
299 osteocytes accumulate at a faster rate than the relative increase in femoral cortical width.
300 Thus, individuals with thicker cortical bone at the posterior quarter of the midshaft diaphysis
301 have a greater density of osteons, but they also have a *proportionally* greater density of
302 osteocyte lacunae. Overall, RMA regression analyses have revealed biological scaling
303 relationships whereby individuals with thicker cortices have *relatively* smaller Haversian
304 canals and osteons combined with a greater density of osteocyte lacunae, compared to
305 individuals with **thinner** femoral cortices.

306

307 **DISCUSSION**

308

309 The aim in this study was to investigate structural relationships between measures of cortical
310 width and robusticity, and histomorphometric variation in the human midshaft femur. Two
311 predictions were tested, evaluating whether macro- and microstructural cortical bone
312 associations can be explained from (1) functional and/or (2) dimensional perspectives. **Our**
313 **analyses reveal that, on average, relative changes in histomorphometric measures of bone**
314 **remodeling products (i.e. secondary osteon tissue) occur in an association with equivalent**
315 **changes in femoral cortical width. These associations are fairly consistent, with a directional,**
316 **allometric, relationship between cortical bone micro- and macro- structures. As** age and sex
317 variation was accounted for in our study (**when undertaking statistical analyses within the**

318 **sub-groups**), these findings support the idea that bone functional adaptation may play a major
319 role in the structural design of femur diaphysis. However, it is impossible to completely rule
320 out inherent intra-specific sex and age variation in human bone metabolism given that this
321 study utilises histomorphometry data from archaeological humans. Our data provide a basis
322 from which to investigate these scaling and functional effects further in experimental
323 contexts.

324 **Functional prediction**

325 Our data are compatible with a biomechanical explanation **of femur size and structure**.
326 Osteon and Haversian canal size became smaller with an increase in cortical width and/or
327 robusticity. However, these trends were not consistent across the entire sample. For example,
328 not only was fragmentary osteon density not significantly associated with Ct.Wi or Ct.Wi.RI,
329 its *r* coefficient also fluctuated between positive and negative between and within age and
330 sex (sub)groups (Tables 2-5, Supplement Table 2). **This may be due to the effects of aging**
331 **and/or sex specific factors underlying bone remodeling in adults**. In all other instances, where
332 results were not significant, the biomechanical prediction was mainly supported.

333

334 The gross structure and geometric properties of a long bone diaphysis are indicators of
335 functional adaptation, and are modeled predominantly during the child and adolescent stages
336 of ontogeny [10, 15, 43]. In most cases, once adulthood is reached, **optimal** mechanical
337 loading is accommodated by targeted remodeling of accrued localised micro-damage by
338 replacing and/or adding new bone [29]. Through a series of positive and negative correlations,
339 along with tests for allometry, the present study supports this functional adaptation of
340 structure in the midshaft human femur. These results agree with basic engineering
341 predictions, and support previous studies of cortical histomorphometric change in relation to
342 strain or mechanical load [e.g. 7, 22-28, 44]. However, it is noted that the sample utilised here
343 relies on mechanical loading inferences through simple measures of bone robusticity.
344 Variation in correlations between the age and sex groups indicates relationships between
345 cortical size and the underlying microstructure are not consistent (Tables 2-5; Supplement
346 Tables 2-3), supporting the well established intra-specific differences in human bone
347 metabolic activity [5]. **There is no doubt that individuals in our sample represent a variety of**
348 **physical activity regimes. There seems to be a clear functional signal in the results in the young**

349 male category, potentially suggesting higher intensity and/or frequency of mechanical load
350 experienced by this group [see 24 for review of behaviours potentially represented by this
351 sample].

352 **Dimensional prediction**

353 The study of allometry in biology has long had important implications for our understanding
354 of structural and functional tissue relationships [45]. It has been of particular importance in
355 studies examining mechanical adaptation of mammalian trabecular bone [46]. However, as
356 identified recently, the assumption that simple intra-specific variation in human skeletal size
357 may be considered to play a role in determining microstructural geometric or other
358 quantitative bone data, is rarely accounted for in research. The present study revealed an
359 isometric relationship between osteon density and cortical robusticity, which supports the
360 idea that larger femora maintain more frequent osteons. However, if only this type of
361 relationship explains the changes in histomorphometric data that accompanies increases in
362 femoral robusticity, then it is unclear why the more robust femora also revealed allometric
363 scaling relationships with bone microstructure. Both Goldman et al [31] and Schlecht and
364 Jepsen [34] previously identified a link between micro- and macro-structure of bone. Our
365 results support their findings, but also highlight the potential effect of localised remodeling
366 on histomorphometry. Similarly to our findings, Goldman et al [31] noted that robust tibiae
367 appear to have more numerous osteons. This micro-macro effect in our study was not
368 consistent across the sample, indicating potential mechanically-induced remodeling may
369 obscure otherwise clear robusticity related relationships. Goldman et al's study [31]
370 examined human tibiae from two different midshaft locations allowing for a broader
371 examination and intra-bone comparison of intra-cortical remodeling, whereas our study
372 focused on sub-periosteal histology from the posterior femoral midshaft only. Thus, the
373 different findings from the two studies are most certainly underlied by variation in sampling
374 location, indicating that remodeling is not constant across intra- and inter-specific cortical
375 sites, bones, and individuals.

376 **Bone structural relationships at the macroscopic and microscopic level are complex**

377 Using geometric properties of osteons and Haversian canals, which are inversely related to
378 strain, our osteon density data could be simply interpreted in a broader mechanical context.

379 While our results support structural bone functional adaptation, it is difficult to exclude the
380 scaling effect of cortical size on histological parameters. This is most clear for osteon densities.
381 Both the intact and total population densities increased in value along with an increase in
382 cortical width and robusticity, which in principle agrees with the first part of both predictions
383 evaluated here. However, given that fragmentary osteon density data did not follow our
384 predictions, and were not significantly correlated with cortical width and/or robusticity
385 either, this may reflect difficulty in distinguishing between scaling versus functional
386 adaptation relationships at the human midshaft femur. **This relationship is likely to be further**
387 **complicated by the effect of aging and sex on the fragmentary osteon density data across the**
388 **sample.** Whilst our RMA regressions attempt to address this, they explain only a portion of
389 the entire data-set, encouraging future research to collect more data. Fragmentary osteon
390 density is a valid proxy for cortical products of bone remodeling because they are remnants
391 of preceding or pre-existing intact osteons [19]. Their increased presence can indicate a
392 higher proportion of cortical bone being remodeled and filled with new osteons. By examining
393 the r coefficients of variation (Tables 2-3), fragmentary osteons were positively correlated
394 with cortical width and robusticity in the entire sample, young adults, middle-aged adults, and
395 young males. The relationship was negative in all the remaining sub-groups. This, however
396 small, deviation from the rest of the results highlights the complexity of functional, structural,
397 and metabolic activity in bone.

398 It is now well established that there is a complementary interaction between genetic,
399 hormonal, dietary, and mechanical factors in regulation of bone remodeling [15]. Of course
400 the results from our skeletal collection do not account for the broad biological picture of bone
401 metabolism. We acknowledge that the standard anthropological age categories are relatively
402 broad and thus may relate to minor osteon number variation with age [47]. In our previous
403 study [24], we also reported histomorphometric variation with social status in this sample
404 related to documented lifestyles [see also 48]. Our conclusions were supported by an
405 evaluation of histological variation adjusted by femoral robusticity index based on midshaft
406 circumference. This showed that femora of similar size in age- and sex- matched humans have
407 different remodeling activity when related to a known behavioural context. Given that the
408 aim in the present study was to seek structural biology relationships (rather than undertaking
409 group comparisons), our present results support these previous conclusions. The complexity

410 of factors behind cortical bone remodeling thus makes it difficult to characterise either
411 biomechanical or dimensional relationships between macro- and microstructure - they are
412 probably complimentary or dependent upon individual/ populational aspects of biology
413 and/or lifestyle. We further acknowledge that it was not possible to measure collagen and
414 mineral content in our study, bone components which are important in facilitating mechanical
415 adaptation [49]. Our finding has methodological implications whereby it seems that data
416 collected either macro- or microscopically alone, may not reflect the complexity of bone form
417 and function relationships.

418 **CONCLUSIONS**

419 This study demonstrates a relationship between femoral size and the underlying histological
420 products of bone growth. The density of osteons, and osteocyte lacunae, increased in more
421 robust femora, and in those with thicker cortical bone. Allometric scaling relationships were
422 also observed. More robust femora with thicker cortical bone also had smaller osteons and
423 Haversian canals, and scaled with negative allometry. These data are compatible with the idea
424 that human femoral macroscopic and microscopic structures are driven by functional
425 adaptation. It is suggested that cortical histomorphometry data examined in future research
426 may benefit from an examination in the light of macroscopic structural measures. Studies
427 aiming to unravel functional adaptation from bone should ideally undertake an integrative
428 approach of macro- (robusticity, size, geometric properties), microscopic (e.g. histological
429 parameters), and strength/ stiffness (mineral density, collagen orientation) variables. Only
430 then a more complete human femur form and function relationship will be understood [50].

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Table 1. Descriptive data for posterior cortical width (Ct.Wi in mm) and femoral robusticity index (Ct.Wi.RI = Ct.Wi/ Max.L x 100).

| Ct.Wi groupings | N | Min | Max | Mean | SD |
|---------------------------|----------|------------|------------|-------------|-----------|
| Entire sample* | 450 | 4.83 | 15.73 | 8.98 | 1.79 |
| Females | 217 | 4.83 | 12.08 | 8.35 | 1.51 |
| Males | 233 | 5.03 | 15.73 | 9.57 | 1.84 |
| Young adults | 126 | 4.83 | 13.35 | 8.71 | 1.77 |
| Middle-aged adults | 319 | 5.03 | 15.73 | 9.08 | 1.80 |
| Old adults | 5 | 6.84 | 10.65 | 9.44 | 1.55 |
| Young females | 77 | 4.83 | 12.08 | 8.06 | 1.58 |
| Middle-aged females | 139 | 5.22 | 11.79 | 8.52 | 1.45 |
| Old females | 1 | 6.84 | 6.84 | 6.84 | - |
| Young males | 49 | 6.01 | 13.35 | 9.73 | 1.58 |
| Middle-aged males | 180 | 5.03 | 15.73 | 9.51 | 1.92 |
| Old males | 4 | 9.32 | 10.65 | 10.09 | .64 |
| Ct.Wi.RI groupings | | | | | |
| Entire sample* | 423 | 1.10 | 3.89 | 2.05 | .40 |
| Females | 206 | 1.13 | 2.92 | 1.99 | .37 |
| Males | 217 | 1.10 | 3.89 | 2.11 | .41 |
| Young adults | 116 | 1.13 | 3.89 | 2.04 | .41 |
| Middle-aged adults | 303 | 1.10 | 3.53 | 2.05 | .39 |
| Young adults | 4 | 2.09 | 2.42 | 2.30 | .14 |
| Young females | 71 | 1.13 | 2.92 | 1.94 | .37 |
| Middle-aged females | 135 | 1.17 | 2.90 | 2.01 | .37 |
| Young males | 45 | 1.28 | 3.89 | 2.19 | .43 |
| Middle-aged males | 168 | 1.10 | 3.53 | 2.09 | .41 |
| Old males | 4 | 2.09 | 2.42 | 2.30 | .14 |

*portion of data from [24: 51-52]

Table 2. Results from Spearman’s correlation tests evaluating histomorphometry data against posterior cortical width (Ct.Wi). Underlined r^2 results indicate weak to moderate correlations, whereas the p values in bold indicate statistical significance < 0.05.

| Variable correlated with Ct.Wi | Statistic | Entire Sample | Females | Males | Young adults | Middle-aged adults | Young females | Young males | Middle-aged females | Middle-aged males |
|--------------------------------|-----------|---------------|---------------|---------------|---------------|--------------------|---------------|---------------|---------------------|-------------------|
| N.On | r | .288 | .216 | .286 | .346 | .249 | .215 | .399 | .191 | .255 |
| | r^2 | 8.29% | 4.67% | 8.18% | <u>11.97%</u> | 6.20% | 4.62% | <u>15.92%</u> | 3.65% | 6.50% |
| | p | .000 | .002 | .000 | .000 | .000 | .063 | .005 | .026 | .001 |
| | n | 443 | 213 | 230 | 124 | 314 | 76 | 48 | 136 | 178 |
| N.On.Fg | r | .023 | -.075 | -.008 | .021 | .003 | -.115 | .213 | -.070 | -.032 |
| | r^2 | 0.05% | 0.56% | 0.64% | 0.04% | 0.00% | 1.32% | 4.54% | 0.49% | 0.10% |
| | p | .647 | .300 | .903 | .820 | .953 | .343 | .155 | .444 | .674 |
| | n | 413 | 193 | 220 | 116 | 292 | 70 | 46 | 122 | 170 |
| OPD | r | .257 | .137 | .223 | .273 | .241 | .090 | .461 | .168 | .195 |
| | r^2 | 6.60% | 1.88% | 4.97% | 7.45% | 5.81% | 0.81% | <u>21.25%</u> | 2.82% | 3.80% |
| | p | .000 | .057 | .001 | .003 | .000 | .460 | .001 | .064 | .011 |
| | n | 413 | 193 | 220 | 116 | 292 | 70 | 46 | 122 | 170 |
| H.Ar | r | -.384 | -.403 | -.338 | -.310 | -.411 | -.226 | -.232 | -.518 | -.347 |
| | r^2 | <u>14.75%</u> | <u>16.24%</u> | <u>11.42%</u> | 9.61% | <u>16.89%</u> | 5.11% | 5.38% | <u>26.83%</u> | <u>12.04%</u> |
| | p | .000 | .000 | .000 | .000 | .000 | .048 | .109 | .000 | .000 |
| | n | 450 | 217 | 233 | 126 | 319 | 77 | 49 | 139 | 180 |
| H.Dm | r | -.451 | -.437 | -.409 | -.412 | -.465 | -.284 | -.402 | -.539 | -.398 |
| | r^2 | <u>20.34%</u> | <u>19.10%</u> | <u>16.73%</u> | <u>16.97%</u> | <u>21.62%</u> | 8.07% | <u>16.16%</u> | <u>29.05%</u> | <u>15.84%</u> |
| | p | .000 | .000 | .000 | .000 | .000 | .012 | .004 | .000 | .000 |
| | n | 450 | 217 | 233 | 126 | 319 | 77 | 49 | 139 | 180 |
| On.Ar | r | -.380 | -.329 | -.365 | -.289 | -.405 | -.137 | -.244 | -.435 | -.374 |
| | r^2 | <u>14.44%</u> | <u>10.82%</u> | <u>13.32%</u> | 8.26% | <u>16.40%</u> | 1.88% | 5.95% | <u>18.92%</u> | <u>13.99%</u> |
| | p | .000 | .000 | .000 | .002 | .000 | .267 | .119 | .000 | .000 |
| | n | 401 | 190 | 211 | 110 | 286 | 68 | 42 | 121 | 165 |
| Ot.Dn | r | .412 | .348 | .410 | .447 | .387 | .234 | .596 | .405 | .355 |
| | r^2 | <u>16.97%</u> | <u>12.11%</u> | <u>16.81%</u> | <u>19.98%</u> | <u>14.98%</u> | 5.48% | <u>35.52%</u> | <u>16.40%</u> | <u>12.60%</u> |
| | p | .000 | .000 | .000 | .000 | .000 | .080 | .000 | .000 | .000 |
| | n | 353 | 161 | 192 | 96 | 252 | 57 | 39 | 103 | 149 |

Table 3. Results from Spearman's correlation tests evaluating histomorphometry data against posterior cortical width robusticity index (Ct.Wi.RI). Underlined r^2 results indicate weak to moderate correlations, whereas the p values in bold indicate statistical significance < 0.05.

| Variable correlated with Ct.Wi.RI | Statistic | Entire Sample | Females | Males | Young adults | Middle-aged adults | Young females | Young males | Middle-aged females | Middle-aged males |
|-----------------------------------|-----------|---------------|---------------|---------------|---------------|--------------------|---------------|---------------|---------------------|-------------------|
| N.On | r | .254 | .264 | .209 | .344 | .208 | .281 | .331 | .234 | .175 |
| | r^2 | 6.45% | 6.97% | 4.37% | <u>11.83%</u> | 4.33% | 7.90% | <u>10.96%</u> | 5.48% | 3.06% |
| | p | .000 | .000 | .002 | .000 | .000 | .018 | .028 | .007 | .024 |
| | n | 416 | 202 | 214 | 114 | 298 | 70 | 44 | 132 | 166 |
| N.On.Fg | r | -.008 | -.041 | -.030 | .030 | -.027 | .004 | .101 | -.089 | -.025 |
| | r^2 | 0.01% | 0.17% | 0.09% | 0.09% | 0.07% | 0.00% | 1.02% | 0.79% | 0.06% |
| | p | .875 | .584 | .674 | .761 | .655 | .972 | .523 | .338 | .755 |
| | n | 387 | 182 | 205 | 106 | 277 | 64 | 42 | 118 | 159 |
| OPD | r | .233 | .236 | .164 | .342 | .193 | .270 | .381 | .211 | .142 |
| | r^2 | 5.43% | 5.57% | 2.69% | <u>11.70%</u> | 3.72% | 7.29% | <u>14.52%</u> | 4.45% | 2.02% |
| | p | .000 | .001 | .019 | .000 | .001 | .031 | .013 | .022 | .074 |
| | n | 387 | 182 | 205 | 106 | 277 | 64 | 42 | 118 | 159 |
| H.Ar | r | -.385 | -.416 | -.331 | -.343 | -.395 | -.292 | -.299 | -.492 | -.318 |
| | r^2 | <u>14.82%</u> | <u>17.31%</u> | <u>10.96%</u> | <u>11.76%</u> | <u>15.60%</u> | 8.53% | 8.94% | <u>24.21%</u> | <u>10.11%</u> |
| | p | .000 | .000 | .000 | .000 | .000 | .014 | .046 | .000 | .000 |
| | n | 423 | 206 | 217 | 116 | 303 | 71 | 45 | 135 | 168 |
| H.Dm | r | -.443 | -.448 | -.404 | -.417 | -.444 | -.322 | -.418 | -.517 | -.379 |
| | r^2 | <u>19.63%</u> | <u>20.07%</u> | <u>16.32%</u> | <u>17.39%</u> | <u>19.71%</u> | <u>10.37%</u> | <u>17.47%</u> | <u>26.73%</u> | <u>14.36%</u> |
| | p | .000 | .000 | .000 | .000 | .000 | .006 | .004 | .000 | .000 |
| | n | 423 | 206 | 217 | 116 | 303 | 71 | 45 | 135 | 168 |
| On.Ar | r | -.345 | -.327 | -.317 | -.252 | -.372 | -.156 | -.160 | -.424 | -.324 |
| | r^2 | <u>11.90%</u> | <u>10.69%</u> | <u>10.05%</u> | 6.35% | <u>13.84%</u> | 2.43% | 2.56% | <u>17.98%</u> | <u>10.50%</u> |
| | p | .000 | .000 | .000 | .011 | .000 | .226 | .332 | .000 | .000 |
| | n | 376 | 179 | 197 | 101 | 271 | 62 | 39 | 117 | 154 |
| Ot.Dn | r | .354 | .297 | .357 | .331 | .352 | .164 | .446 | .376 | .317 |
| | r^2 | <u>12.53%</u> | 8.82% | <u>12.74%</u> | <u>10.96%</u> | <u>12.39%</u> | 2.69% | <u>19.89%</u> | <u>14.14%</u> | <u>10.05%</u> |
| | p | .000 | .000 | .000 | .002 | .000 | .249 | .006 | .000 | .000 |
| | n | 330 | 150 | 180 | 88 | 238 | 51 | 37 | 99 | 139 |

Table 4. Results from Reduced Major Axis (RMA) regression tests for all significant and “strongest” correlations as identified in Table 3 (also see Figure 2), where histology data are regressed against Ct.Wi.

| RMA regression x = Ct.Wi | Slope (b) | r² | 95% CI slope | intercept | p | Relationship b >1: positive allometry b = 1: isometric growth b <1: negative allometry |
|-------------------------------------|------------------|----------------------|---------------------|------------------|----------|---|
| y = N.On | | | | | | |
| Young adults | 1.075 | 0.073 | 0.840, 1.277 | 0.092 | 0.002 | isometric growth |
| Young males | 1.543 | 0.107 | 0.985, 4.980 | -0.409 | 0.022 | “ |
| y = OPD | | | | | | |
| Young males | 1.060 | 0.230 | 0.690, 1.328 | 0.205 | 0.001 | isometric growth |
| y = H.Ar | | | | | | |
| Entire sample | -3.781 | 0.110 | -4.106, -3.434 | 6.508 | 0.000 | negative allometry |
| Females | -3.678 | 0.132 | -4.085, -3.168 | 6.613 | 0.000 | “ |
| Males | -4.267 | 0.100 | -4.800, -3.644 | 7.368 | 0.000 | “ |
| Middle-aged adults | -3.900 | 0.130 | -4.282, -3.438 | 6.950 | 0.000 | “ |
| Middle-aged females | -3.905 | 0.256 | -4.432, -3.262 | 6.849 | 0.000 | “ |
| Middle-aged males | -4.113 | 0.096 | -4.674, -3.450 | 7.243 | 0.000 | “ |
| y = H.Dm | | | | | | |
| Entire sample | -1.736 | 0.159 | -1.887, -1.574 | 3.292 | 0.000 | negative allometry |
| Females | -1.667 | 0.198 | -1.863, -1.448 | 3.192 | 0.000 | “ |
| Males | -1.963 | 0.124 | -2.215, -1.669 | 3.547 | 0.000 | “ |
| Young adults | -1.555 | 0.169 | -1.763, -1.291 | 3.096 | 0.000 | “ |
| Middle-aged adults | -1.816 | 0.156 | -2.001, -1.601 | 3.380 | 0.000 | “ |
| Young males | -1.754 | 0.163 | -2.139, -1.196 | 3.326 | 0.004 | “ |
| Middle-aged females | -1.716 | 0.281 | -1.960, -1.423 | 3.247 | 0.000 | “ |
| Middle-aged males | -1.970 | 0.113 | -2.277, -1.596 | 3.561 | 0.000 | “ |
| y = On.Ar | | | | | | |
| Entire sample | -2.944 | 0.110 | -3.209, -2.625 | 7.149 | 0.000 | negative allometry |
| Females | -3.261 | 0.092 | -3.723, -2.713 | 7.362 | 0.000 | “ |
| Males | -3.045 | 0.121 | -3.394, -2.650 | 7.315 | 0.000 | “ |
| Middle-aged adults | -3.060 | 0.121 | -3.392, -2.673 | 7.276 | 0.000 | “ |
| Middle-aged females | -3.556 | 0.148 | -4.231, -2.769 | 7.644 | 0.000 | “ |
| Middle-aged males | -2.965 | 0.124 | -3.312, -2.517 | 7.249 | 0.000 | “ |
| y = Ot.Dn | | | | | | |
| Entire sample | 1.604 | 0.137 | 1.431, 1.755 | 1.273 | 0.000 | positive allometry |
| Females | 1.535 | 0.107 | 1.250, 1.767 | 1.372 | 0.000 | “ |
| Males | 1.825 | 0.137 | 1.562, 2.056 | 1.026 | 0.000 | “ |
| Young adults | 1.609 | 0.177 | 1.211, 1.892 | 1.297 | 0.000 | “ |
| Middle-aged adults | 1.601 | 0.122 | 1.410, 1.770 | 1.264 | 0.000 | “ |
| Young males | 2.081 | 0.291 | 1.362, 2.623 | 0.800 | 0.000 | “ |
| Middle-aged females | 1.516 | 0.166 | 1.217, 1.751 | 1.384 | 0.000 | “ |
| Middle-aged males | 1.745 | 0.108 | 1.445, 1.994 | 1.095 | 0.000 | “ |

Table 5. Results from reduced major axis (RMA) regression tests for all significant and “strongest” correlations as identified in Table 4 (also see Figure 3), where histology data are regressed against Ct.Wi.RI.

| RMA regression x = Ct.Wi.RI | Slope (b) | r² | 95% CI slope | intercept | p | Relationship b > 1: positive allometry b = 1: isometric growth b < 1: negative allometry |
|--|------------------|----------------------|---------------------|------------------|----------|---|
| x = N.On | | | | | | |
| Young adults | 1.124 | 0.060 | 0.815, 1.366 | 0.752 | 0.007 | isometric growth |
| Young males | 1.390 | 0.049 | 0.696, 4.457 | 0.638 | 0.162 | “ |
| x = OPD | | | | | | |
| Young adults | 0.892 | 0.109 | 0.678, 1.070 | 0.960 | 0.000 | isometric growth |
| Young males | 0.883 | 0.100 | 0.410, 1.191 | 0.949 | 0.045 | “ |
| x = H.Ar | | | | | | |
| Entire sample | -3.890 | 0.125 | -4.240, -3.497 | 4.407 | 0.000 | negative allometry |
| Females | -3.553 | 0.148 | -3.964, -3.046 | 4.280 | 0.000 | “ |
| Males | -4.236 | 0.105 | -4.772, -3.580 | 4.545 | 0.000 | “ |
| Young adults | -3.568 | 0.094 | -4.156, -2.757 | 4.283 | 0.000 | “ |
| Middle-aged adults | -3.969 | 0.135 | -4.389, -3.507 | 4.444 | 0.000 | “ |
| Middle-aged females | -3.696 | 0.229 | -4.186, -3.132 | 4.329 | 0.000 | “ |
| Middle-aged males | -4.171 | 0.093 | -4.783, -3.398 | 4.536 | 0.000 | “ |
| x = H.Dm | | | | | | |
| Entire sample | -1.783 | 0.170 | -1.952, -1.593 | 2.190 | 0.000 | negative allometry |
| Females | -1.635 | 0.205 | -1.840, -1.400 | 2.141 | 0.000 | “ |
| Males | -1.925 | 0.134 | -2.177, -1.600 | 2.241 | 0.000 | “ |
| Young adults | -1.609 | 0.178 | -1.866, -1.280 | 2.132 | 0.000 | “ |
| Middle-aged adults | -1.844 | 0.164 | -2.034, -1.560 | 2.212 | 0.000 | “ |
| Young females | -1.637 | 0.124 | -1.980, -1.213 | 2.134 | 0.003 | “ |
| Young males | -1.626 | 0.180 | -2.042, -0.935 | 2.146 | 0.003 | “ |
| Middle-aged females | -1.642 | 0.261 | -1.887, -1.350 | 2.147 | 0.000 | “ |
| Middle-aged males | -2.033 | 0.087 | -2.327, -1.663 | 2.275 | 0.000 | “ |
| x = On.Ar | | | | | | |
| Entire sample | -2.986 | 0.103 | -3.274, -2.643 | 5.266 | 0.000 | negative allometry |
| Females | -3.081 | 0.092 | -3.526, -2.546 | 5.269 | 0.000 | “ |
| Males | -2.968 | 0.104 | -3.342, -2.521 | 5.283 | 0.000 | “ |
| Middle-aged adults | -3.098 | 0.122 | -3.425, -2.682 | 5.304 | 0.000 | “ |
| Middle-aged females | -3.437 | 0.123 | -4.083, -2.620 | 5.371 | 0.000 | “ |
| Middle-aged males | -2.994 | 0.081 | -3.390, -2.523 | 5.291 | 0.000 | “ |
| x = Ot.Dn | | | | | | |
| Entire sample | 1.611 | 0.112 | 1.416, 1.782 | 2.303 | 0.000 | positive allometry |
| Males | 1.718 | 0.114 | 1.429, 1.953 | 2.267 | 0.000 | “ |
| Young adults | 1.633 | 0.100 | 1.130, 2.001 | 2.300 | 0.004 | “ |
| Middle-aged adults | 1.595 | 0.113 | 1.385, 1.775 | 2.307 | 0.000 | “ |
| Young males | 1.754 | 0.131 | 0.833, 2.330 | 2.262 | 0.029 | “ |
| Middle-aged females | 1.418 | 0.145 | 1.177, 1.626 | 2.365 | 0.000 | “ |
| Middle-aged males | 1.805 | 0.090 | 1.471, 2.064 | 2.231 | 0.000 | “ |

Supplement Table 1. Descriptive data for ratio values of histology variables.

| Grouping | Histology variable ratio | N | Min | Max | Mean | SD |
|---------------------|---------------------------------|----------|------------|------------|-------------|-----------|
| Entire sample | H.Ar: On.Ar | 401 | .007 | .670 | .0889 | .0621 |
| | N.On: OPD | 413 | .293 | 1.093 | .719 | .078 |
| | Ot.Dn: OPD | 351 | 10.222 | 95.731 | 35.113 | 11.352 |
| | Ot.Dn: On.Ar | 351 | .004 | .403 | .0386 | .0390 |
| Females | H.Ar: On.Ar | 190 | .007 | .670 | .086 | .0618 |
| | N.On: OPD | 193 | .467 | 1.093 | .729 | .0740 |
| | Ot.Dn: OPD | 160 | 10.971 | 95.731 | 34.838 | 11.241 |
| | Ot.Dn: On.Ar | 161 | .004 | .403 | .0345 | .0426 |
| Males | H.Ar: On.Ar | 211 | .026 | .618 | .091 | .062 |
| | N.On: OPD | 220 | .293 | .856 | .710 | .081 |
| | Ot.Dn: OPD ¹ | 191 | 10.222 | 67.895 | 35.343 | 11.470 |
| | Ot.Dn: On.Ar | 190 | .004 | .217 | .0420 | .0355 |
| Young adults | H.Ar: On.Ar | 110 | .007 | .220 | .0817 | .0403 |
| | N.On: OPD | 116 | .293 | .889 | .730 | .0849 |
| | Ot.Dn: OPD | 95 | 10.971 | 95.731 | 39.203 | 13.191 |
| | Ot.Dn: On.Ar | 94 | .006 | .130 | .0363 | .0282 |
| Middle-aged adults | H.Ar: On.Ar | 286 | .023 | .670 | .0917 | .0683 |
| | N.On: OPD | 292 | .418 | 1.093 | .714 | .0752 |
| | Ot.Dn: OPD | 251 | 10.222 | 65.641 | 33.574 | 10.212 |
| | Ot.Dn: On.Ar | 252 | .004 | .403 | .0385 | .0410 |
| Old adults | H.Ar: On.Ar | 5 | .029 | .231 | .079 | .085 |
| | N.On: OPD | 5 | .712 | .812 | .753 | .037 |
| | Ot.Dn: OPD | 5 | 19.146 | 46.417 | 34.655 | 11.154 |
| | Ot.Dn: On.Ar | 5 | .010 | .217 | .086 | .078 |
| Young females | H.Ar: On.Ar | 68 | .007 | .194 | .081 | .039 |
| | N.On: OPD | 70 | .501 | .889 | .730 | .081 |
| | Ot.Dn: OPD | 57 | 10.971 | 95.731 | 37.148 | 14.622 |
| | Ot.Dn: On.Ar | 57 | .006 | .118 | .028 | .022 |
| Middle-aged females | H.Ar: On.Ar | 121 | .023 | .670 | .090 | .072 |
| | N.On: OPD | 122 | .467 | 1.093 | .728 | .070 |
| | Ot.Dn: OPD ¹ | 102 | 19.160 | 60.817 | 33.700 | 8.580 |
| | Ot.Dn: On.Ar | 103 | .004 | .403 | .038 | .050 |
| Old females | H.Ar: On.Ar | 1 | .047 | .047 | .047 | N/A |
| | N.On: OPD | 1 | .758 | .758 | .758 | |
| | Ot.Dn: OPD | 1 | 19.146 | 19.146 | 19.146 | |
| | Ot.Dn: On.Ar | 1 | .010 | .010 | .010 | |
| Young males | H.Ar: On.Ar | 42 | .026 | .220 | .0835 | .043 |
| | N.On: OPD | 46 | .293 | .846 | .730 | .091 |
| | Ot.Dn: OPD ² | 38 | 26.046 | 67.895 | 42.285 | 10.110 |
| | Ot.Dn: On.Ar | 37 | .009 | .130 | .049 | .0319 |
| Middle-aged males | H.Ar: On.Ar | 165 | .027 | .618 | .093 | .066 |
| | N.On: OPD | 170 | .418 | .856 | .704 | .078 |
| | Ot.Dn: OPD ¹ | 149 | 10.222 | 65.641 | 33.487 | 11.220 |
| | Ot.Dn: On.Ar | 149 | .004 | .182 | .039 | .033 |
| Old males | H.Ar: On.Ar | 4 | .029 | .231 | .087 | .097 |
| | N.On: OPD | 4 | .712 | .812 | .752 | .043 |
| | Ot.Dn: OPD | 4 | 29.396 | 46.417 | 38.532 | 8.103 |
| | Ot.Dn: On.Ar | 4 | .057 | .217 | .104 | .076 |

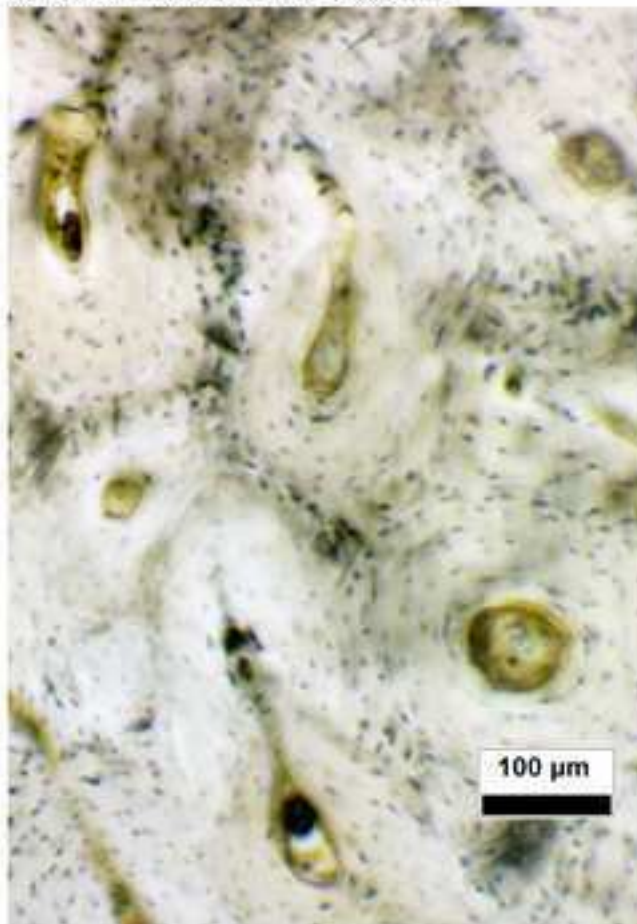
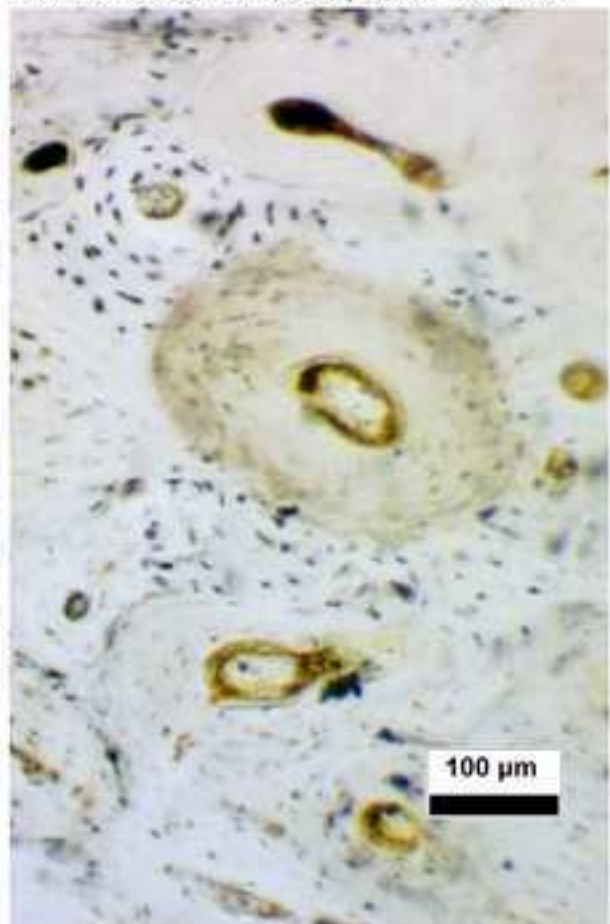
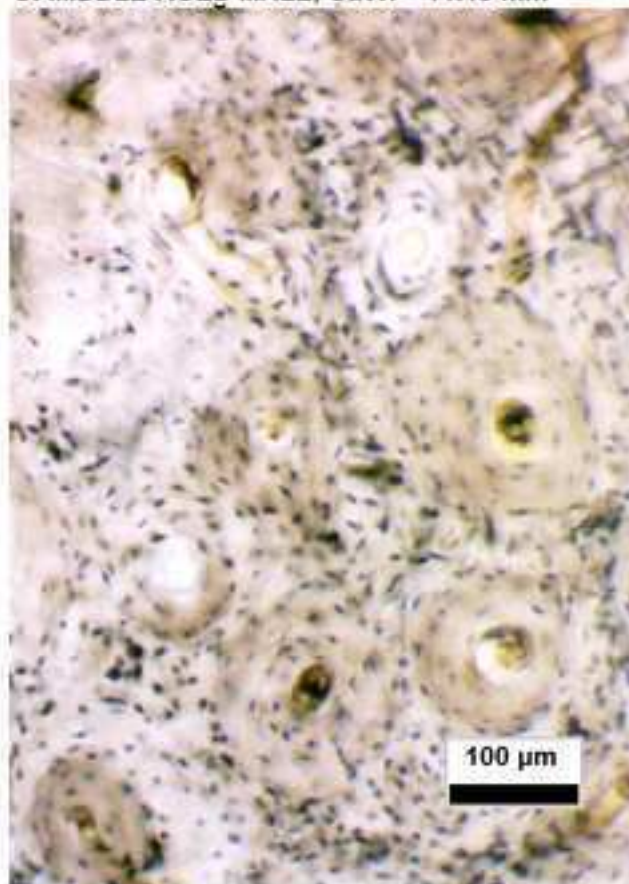
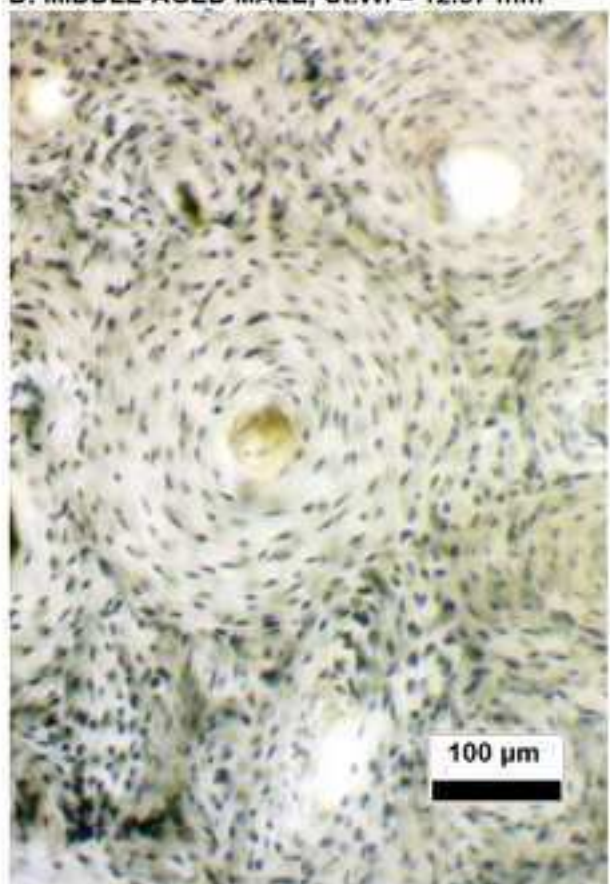
¹ Normally distributed data in this grouping (Kolmogorov-Smirnov normality test $p > .05$)² Normally distributed data in this grouping (Shapiro-Wilk normality test $p > .05$)

Supplement Table 2. Results from Spearman’s and Pearson’s (¹) correlation tests evaluating histomorphometry ratio data against posterior cortical width (Ct.Wi), and posterior cortical width robusticity index (Ct.Wi.RI). Underlined r^2 results indicate weak to moderate correlations, whereas the p values in bold indicate statistical significance < 0.05.

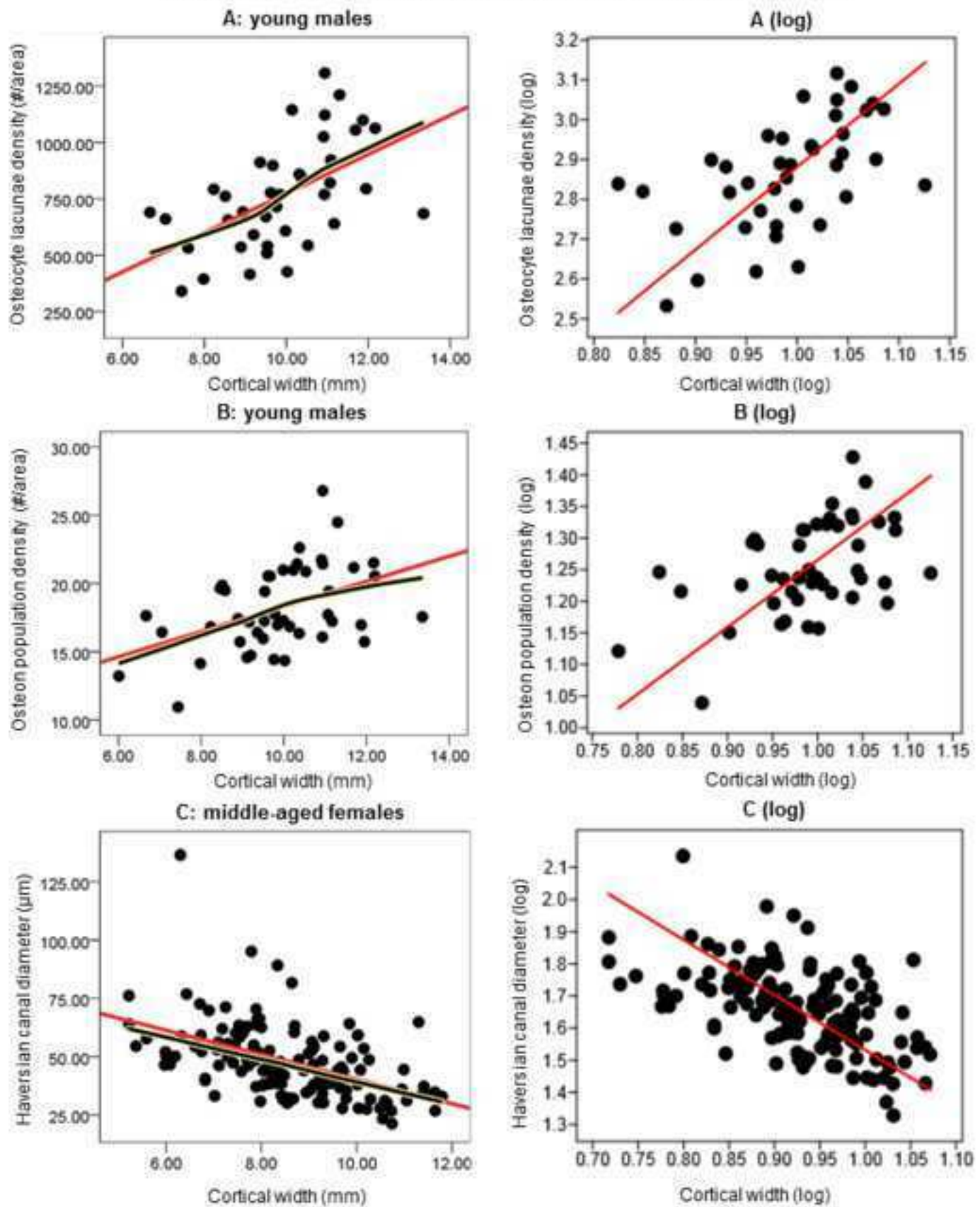
| Ratio histology variable correlated with Ct.Wi | Statistic | Entire Sample | Females | Males | Young adults | Middle-aged adults | Young females | Young males | Middle-aged females | Middle-aged males |
|--|-----------|---------------|---------------|-------------------|---------------|--------------------|---------------|-------------------|---------------------|-------------------|
| H.Ar: On.Ar | r | -.132 | -.183 | -.134 | -.137 | -.140 | -.080 | -.252 | -.251 | -.100 |
| | r^2 | 1.74% | 3.35% | 1.80% | 1.88% | 1.96% | 0.64% | 6.35% | 6.30% | 1% |
| | p | .008 | .011 | .052 | .153 | .018 | .515 | .107 | .005 | .200 |
| | n | 401 | 190 | 211 | 110 | 286 | 68 | 42 | 121 | 165 |
| N.On: OPD | r | .139 | .131 | .182 | .148 | .144 | .114 | .091 | .153 | .181 |
| | r^2 | 1.93% | 1.72% | 3.31% | 2.19% | 2.07% | 1.30% | 0.83% | 2.34% | 3.28% |
| | p | .000 | .069 | .007 | .112 | .014 | .349 | .548 | .092 | .018 |
| | n | 351 | 193 | 220 | 116 | 292 | 70 | 46 | 122 | 170 |
| Ot.Dn: OPD | r | .293 | .281 | .169 ¹ | .382 | .272 | .251 | .411 ¹ | .268 ¹ | .220 ¹ |
| | r^2 | 8.58% | 7.90% | 2.86% | <u>14.59%</u> | 7.40% | 6.30% | <u>16.89%</u> | 7.18% | 4.84% |
| | p | .000 | .000 | .032 | .000 | .000 | .060 | .010 | .007 | .007 |
| | n | 351 | 160 | 160 | 95 | 251 | 57 | 38 | 102 | 149 |
| Ot.Dn: On.Ar | r | .444 | .349 | .445 | .409 | .446 | .172 | .447 | .439 | .432 |
| | r^2 | <u>19.71%</u> | <u>12.18%</u> | <u>19.80%</u> | <u>16.73%</u> | <u>19.89%</u> | 2.96% | <u>19.98%</u> | <u>19.27%</u> | <u>18.66%</u> |
| | p | .000 | .000 | .000 | .000 | .000 | .201 | .006 | .000 | .000 |
| | n | 351 | 161 | 190 | 94 | 252 | 57 | 37 | 103 | 149 |
| Ratio histology variable correlated with Ct.Wi.RI | | | | | | | | | | |
| H.Ar: On.Ar | r | -.174 | -.196 | -.161 | -.200 | -.159 | -.095 | -.362 | -.235 | -.097 |
| | r^2 | 3.03% | 3.84% | 2.59% | 4% | 2.53% | 0.90% | <u>13.10%</u> | 5.52% | 0.94% |
| | p | .001 | .009 | .024 | .044 | .009 | .464 | .023 | .011 | .232 |
| | n | 376 | 179 | 197 | 101 | 271 | 62 | 39 | 117 | 154 |
| N.On: OPD | r | .154 | .132 | .180 | .122 | .166 | .043 | .112 | .199 | .164 |
| | r^2 | 2.37% | 1.74% | 3.24% | 1.49% | 2.76% | 0.18% | 1.25% | 3.96% | 2.69% |
| | p | .002 | .076 | .010 | .212 | .006 | .735 | .480 | .030 | .039 |
| | n | 387 | 182 | 205 | 106 | 277 | 64 | 42 | 118 | 159 |
| Ot.Dn: OPD | r | .246 | .184 | .082 ¹ | .240 | .253 | .090 | .287 ¹ | .205 ¹ | .217 ¹ |
| | r^2 | 6.05% | 3.39% | 0.67% | <u>5.76%</u> | 6.40% | 0.81% | <u>8.24%</u> | 4.11% | 4.71% |
| | p | .000 | .025 | .317 | .025 | .000 | .532 | .089 | .043 | .010 |
| | n | 328 | 149 | 149 | 87 | 237 | 51 | 36 | 98 | 139 |
| Ot.Dn: On.Ar | r | .387 | .331 | .380 | .324 | .399 | .156 | .306 | .424 | .371 |
| | r^2 | <u>14.98%</u> | <u>10.96%</u> | <u>14.44%</u> | <u>10.50%</u> | <u>15.92%</u> | 2.43% | 9.36% | <u>17.98%</u> | <u>13.76%</u> |
| | p | .000 | .000 | .000 | .002 | .000 | .275 | .073 | .000 | .000 |
| | n | 328 | 150 | 178 | 86 | 238 | 51 | 35 | 99 | 139 |

Supplement Table 3. Results from Reduced Major Axis (RMA) regression tests for all significant and “strongest” correlations identified in Supplement Table 2, where histology ratio data are regressed against Ct.WI and Ct.WI.RI.

| RMA regression x = Ct.Wi | Slope (b) | r² | 95% CI slope | intercept | p | Relationship b > 1: positive allometry b = 1: isometric growth b < 1: negative allometry |
|-------------------------------------|------------------|----------------------|---------------------|------------------|----------|---|
| x = Ot.Dn: OPD | | | | | | |
| Young adults | 1.579 | 0.093 | 1.141, 1.934 | 0.090 | 0.003 | positive allometry |
| Young males | 1.601 | 0.156 | 0.945, 2.041 | 0.019 | 0.017 | isometric growth |
| x = Ot.Dn: On.Ar | | | | | | |
| Entire Sample | 4.235 | 0.156 | 3.783, 4.626 | -5.589 | 0.000 | positive allometry |
| Females | 4.455 | 0.107 | 3.642, 5.110 | -5.696 | 0.000 | “ |
| Males | 4.549 | 0.173 | 3.884, 5.103 | -5.987 | 0.000 | “ |
| Young adults | 3.784 | 0.151 | 2.986, 4.934 | -5.115 | 0.000 | “ |
| Middle-aged adults | 4.353 | 0.154 | 3.806, 4.822 | -5.726 | 0.000 | “ |
| Young males | 4.765 | 0.189 | 2.945, 5.983 | -6.146 | 0.007 | “ |
| Middle-aged females | 4.884 | 0.161 | 3.801, 5.741 | -6.097 | 0.000 | “ |
| Middle-aged males | 4.366 | 0.162 | 3.693, 4.921 | -5.820 | 0.000 | “ |
| RMA regression y = Ct.Wi.RI | | | | | | |
| x = H.Ar: On.Ar | | | | | | |
| Young males | -2.621 | 0.153 | -3.327, -1.353 | -0.242 | 0.014 | negative allometry |
| x = Ot.Dn: On.Ar | | | | | | |
| Entire Sample | 4.303 | 0.133 | 3.802, 4.723 | -2.881 | 0.000 | positive allometry |
| Females | 4.272 | 0.099 | 3.520, 4.941 | -2.858 | 0.000 | “ |
| Males | 4.365 | 0.143 | 3.664, 4.916 | -2.912 | 0.000 | “ |
| Young adults | 3.826 | 0.086 | 2.806, 4.591 | -2.744 | 0.006 | “ |
| Middle-aged adults | 4.403 | 0.147 | 3.868, 4.897 | -2.912 | 0.000 | “ |
| Middle-aged females | 4.614 | 0.160 | 3.694, 5.415 | -2.945 | 0.000 | “ |
| Middle-aged males | 4.311 | 0.137 | 3.544, 4.891 | -2.905 | 0.000 | “ |

A: YOUNG MALE, Ct. Wi = 9.62 mm**B: MIDDLE-AGED FEMALE, Ct.Wi = 8.17 mm****C: MIDDLE-AGED MALE, Ct.Wi = 11.19 mm****D: MIDDLE-AGED MALE, Ct.Wi = 12.57 mm**

EXAMPLES OF RAW DATA CORRELATIONS (A-C) AND THEIR LOG-TRANSFORMED REDUCED MAJOR AXIS REGRESSIONS (A-C LOG) FOR CORTICAL WIDTH AND HISTOLOGY DATA



EXAMPLES OF RAW DATA CORRELATIONS (A-C) AND THEIR LOG-TRANSFORMED REDUCED MAJOR AXIS REGRESSIONS (A-C LOG) FOR CORTICAL WIDTH ROBUSTICITY INDEX AND HISTOLOGY DATA

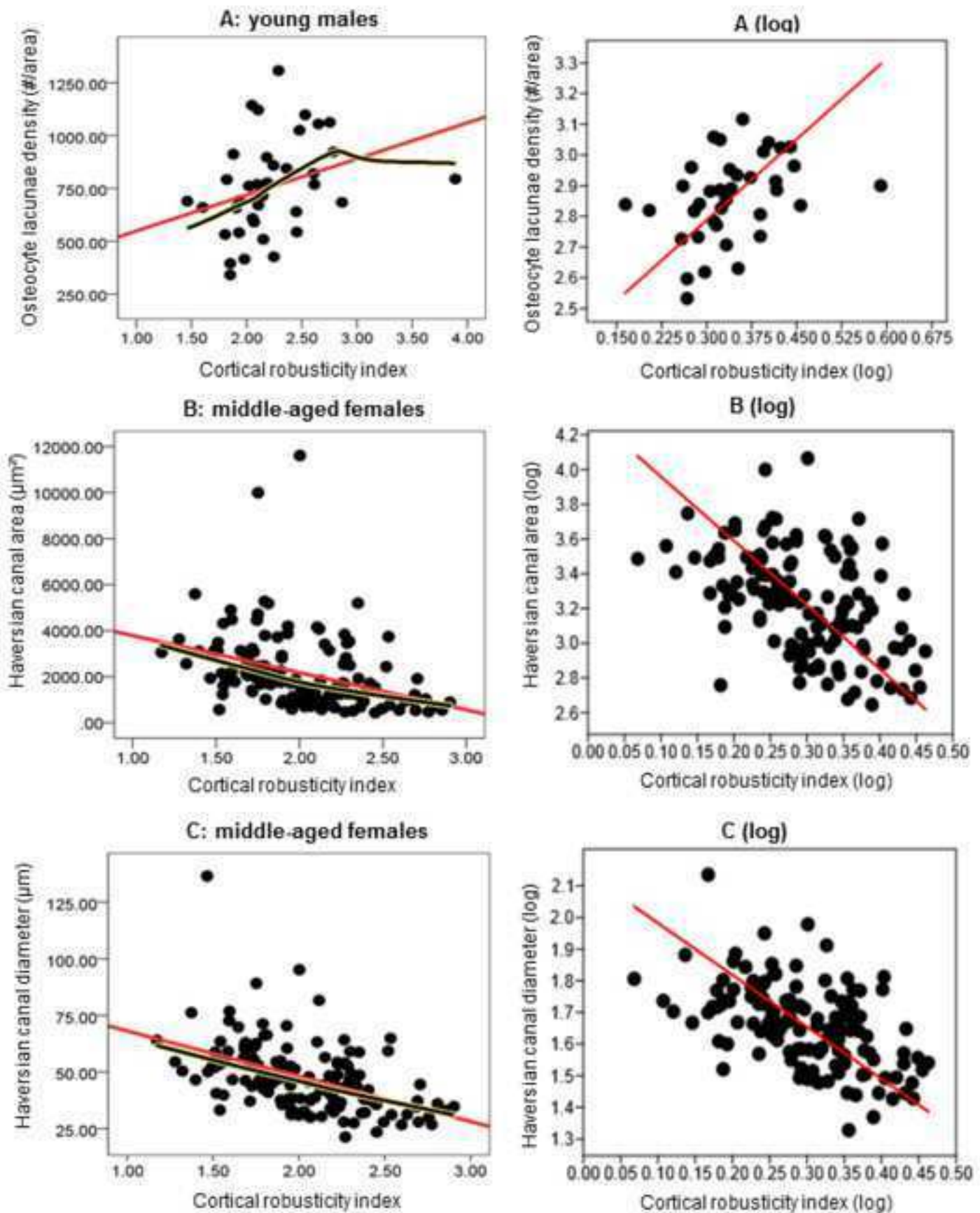


Figure 1.

A series of images illustrating variation (with age-at-death, sex, and measures of cortical width/robusticity) in osteon and osteocyte lacunae densities, and Haversian canal and osteon size in the present sample of sub-periosteal posterior human midshaft femoral sections.

Figure 2.

A series of “strong” (see Table 2) simple correlations (raw data, A-C), and their log-transformed Reduced Major Axis regressions (A-C log, see Table 4), indicating negative and positive relationships between femoral cortical width and histology data.

Figure 3.

A series of “strong” (see Table 3) simple correlations (raw data, A-C), and their log-transformed Reduced Major Axis regressions (A-C log, see Table 5), indicating negative and positive relationships between femoral cortical width robusticity index and cortical histology data.