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Heritability and Genetic Correlations for Bone Microarchitecture: The Framingham Study Families

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Abstract

High-resolution peripheral quantitative computed tomography (HR-pQCT) measures bone microarchitecture and volumetric bone mineral density (vBMD), important risk factors for osteoporotic fractures. We estimated the heritability (h^2) of bone microstructure indices and vBMD, measured by HR-pQCT, and genetic correlations (ρ_G) among them and between them and regional aBMD measured by dual-energy X-ray absorptiometry (DXA), in adult relatives from the Framingham Heart Study. Cortical (Ct) and trabecular (Tb) traits were measured at the distal radius and tibia in up to 1047 participants, and ultradistal radius (UD) aBMD was obtained by DXA. Heritability estimates, adjusted for age, sex, and estrogenic status (in women), ranged from 19.3% (trabecular number) to 82.8% ($p < 0.01$, Ct.vBMD) in the radius and from 51.9% (trabecular thickness) to 98.3% (cortical cross-sectional area fraction) in the tibia. Additional adjustments for height, weight, and radial aBMD had no major effect on h^2 estimates. In bivariate analyses, moderate to high genetic correlations were found between radial total vBMD and microarchitecture traits (ρ_G from 0.227 to 0.913), except for cortical porosity. At the tibia, a similar pattern of genetic correlations was observed (ρ_G from 0.274 to 0.948), except for cortical porosity. Environmental correlations between the microarchitecture traits were also substantial. There were high genetic correlations between UD aBMD and multivariable-adjusted total and trabecular vBMD at the radius (ρ_G = 0.811 and 0.917, respectively). In summary, in related men and women from a population-based cohort, cortical and trabecular microarchitecture and vBMD at the radius and tibia were heritable and shared some h^2 with regional aBMD measured by DXA.

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Disclosures

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These findings of high heritability of HR-pQCT traits, with a slight attenuation when adjusting for aBMD, supports further work to identify the specific variants underlying volumetric bone density and fine structure of long bones. Knowledge that some of these traits are genetically correlated can serve to reduce the number of traits for genetic association studies.

Keywords

BONE QCT/MICRO–CT; GENERAL POPULATION STUDIES; GENETIC EPIDEMIOLOGICAL STUDY; HERITABILITY; CORTICAL POROSITY

Introduction

Genetic factors contribute to the risk of osteoporotic fractures, which is a growing health problem as the population is aging.[1] At the present, areal bone mineral density (aBMD) measured by dual-energy X-ray absorptiometry (DXA) is considered to be the best proxy phenotype for risk of fractures. Based on aBMD correlating highly with bone strength, it has been used as a phenotype for multiple previous genetic studies; however, it does not capture aspects of bone structure and bone strength that may contribute to fracture risk, such as bone size, shape, and trabecular and cortical density and morphology. aBMD is characterized by high heritability (h^2), estimated to be 45% to 78% depending upon the skeletal site and age.[2,3] However, there is evidence that aBMD does not capture all of the genetic contributions to osteoporotic fractures.[4–6] Moreover, in spite of the strong heritable component of aBMD, the genes identified in genome-wide association studies (GWAS) so far overlap only to some degree with the fracture phenotype.[7]

The recent availability of high-resolution peripheral quantitative computed tomography (HR-pQCT) makes it possible to measure bone microarchitecture and volumetric bone mineral density (vBMD) in vivo.[8] It provides measures of both trabecular and cortical traits, which differ between fracture cases and controls and thus may be important predictors of fracture.[9–11] Indeed, numerous cross-sectional case-control studies have shown that HR-pQCT measurements are associated with prevalent fragility fracture independent of aBMD (reviewed in Cheung and colleagues[8]). Despite the uniqueness of bone microarchitecture measures, they do correlate moderately with traditional aBMD measures.[12] For instance, Sornay-Rendu reported good agreement between ultradistal radius aBMD and densities and microstructure obtained by HR-pQCT at the same site (from 0.54 to 0.85[13]). Correlations were also significant but weaker for HR-pQCT of the distal tibia and aBMD of the hip.

Despite these correlations between measures of bone density and architecture, there are no data that indicate to what extent phenotypic correlations between the microarchitecture, vBMD, and aBMD measures reflect potential pleiotropic effects of genes. Because we reported earlier that most of the phenotypic similarity between quantitative bone phenotypes (such as aBMD, hip geometry, and heel ultrasound metrics) is driven by their sharing of associated genetic variants,[14] this knowledge may prove helpful in defining the best phenotypes to be used in the planning of genetic studies of these novel measures.

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Several recent studies supported the hypothesis that HR-pQCT-derived bone microarchitecture and vBMD traits are heritable. Nagy and colleagues[15] noted the familial resemblance of bone microarchitecture parameters between postmenopausal mothers and their premenopausal daughters. Further, in an analysis of 432 subjects from the Geneva Retiree Cohort and their adult offspring (n = 96), Bonnet and colleagues[16] estimated that heritability values for bone microstructural traits at the distal radius and tibia ranged from 22% to 64%. Most recently, Bjornerem and colleagues[11] measured HR-pQCT indices in 95 monozygotic (MZ) and 66 dizygotic (DZ) white female twin pairs around menopause. The proportion of variance accounted for by genetic factors was substantial, and differences in genetic factors contributed to variability of HR-pQCT traits more than differences in the women's environment.[11] These family-based studies of HR-pQCT measures have used only modest samples of women and even smaller samples of men. Also, there are few data on whether the genetic variance captured by compartment-specific vBMD, porosity, and bone microarchitecture measured with HR-pQCT is independent of that for conventional aBMD. We, therefore, hypothesized that: 1) heritable factors are responsible for most of the variance in HR-pQCT traits; and 2) this variance is independent from conventional aBMD. We report here a dissection of interrelations between bone phenotypes measured using both DXA and HR-pQCT using a family-based community sample.

Materials and Methods

Sample

Participants include a subsample of the community-based Framingham Offspring Study Cohort who had valid bone microarchitecture measured at the radius or tibia,[17] using HR-pQCT, which is part of an ongoing study. To be eligible for this analysis, participants with these measures had to have at least one family member with HR-pQCT measures. The Offspring Cohort of the Framingham Heart Study was initially recruited in 1971. In brief, the Framingham Offspring Cohort comprises adult members of two-generational (mostly nuclear) families of European ancestry. Details and descriptions of the Framingham Osteoporosis Study, in particular family samples with bone phenotypes available for the analyses, were provided elsewhere,[18,19] as well as publicly available through the Database of Genotype and Phenotype (dbGaP) at http://view.ncbi.nlm.nih.gov/dbgap.

Participants who attended the ninth index Offspring exam (2011–2014) were invited to come back to attend the Osteoporosis Study call-back exam and have measurements of bone by HR-pQCT as well as DXA aBMD of the hip and distal forearm. The sample included up to 1047 participants who had aBMD and HR-pQCT measurements and who were members of pedigrees (mostly sibling [247], avuncular [11], and first cousins [109] pairs). All study procedures were approved by the Hebrew SeniorLife Institutional Review Board as well as the Framingham Study Executive Committee and Observational Study Monitoring Board. All participants provided informed consent.

Osteoporosis-related skeletal phenotypes

To measure aBMD, The participants underwent bone densitometry by DXA at the hip, spine, and forearm with a Lunar DPX-L (Lunar Corp., Madison, WI, USA) between March 2012

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and September 2014. Following long-standing procedures, the non-dominant forearm was scanned, unless the participant had a previous adult fracture, in which case the contralateral side was scanned. If participants had fractures on both sides, the site with oldest fracture was scanned. The side was determined by asking which hand was usually used for writing and then the opposite side was scanned. The left side was scanned for participants answering that both sides were used equally. The coefficient of variation (CV) in normal subjects for the ultradistal (UD) aBMD by DPX-L was 2.7%. The distal-tibia aBMD was not directly measured using the DXA scanner.

Bone microarchitecture measurements

HR-pQCT was performed at the ultradistal radius and tibia using the Xtreme CT (Scanco Medical AG, Brüttisellen, Switzerland), following previously published methods.[9,20] HR-pQCT was performed on the radius at the non-dominant side and on the right tibia, unless the participant had a previous adult fracture, in which case the contralateral side was scanned.

Analyses and QA

Using Scanco software (version 6.0), the standard analysis of images and extended cortical analyses[21] were performed by one technologist and reviewed for quality by senior team members. Data capture was supported by RedCaP.[22]

Scans were evaluated for movement using a five-point scale (1 lowest to 5 highest); scans evaluated as grade 5 were excluded because of extreme movement. For scans with grade 4, trabecular and cortical microstructure were excluded, but volumetric density as well as total, cortical, and trabecular areas were included.[23] The following bone microarchitecture traits were obtained from the distal radius and tibia: total density (Tt.vBMD, mg/cm^3 HA); cortical density (Ct.vBMD, mg/cm^3 HA); cortical porosity (Ct.Po, %); cortical thickness (Ct.Th, mm); trabecular density (Tb.vBMD, mg/cm^3 HA); trabecular number (Tb.N, mm^{-1}), and trabecular thickness (Tb.Th, mm). Cortical cross-sectional area (Ct.Ar, mm^2) and total cross-sectional area (Tt.Ar, mm^2) were measured and used to calculate cortical area fraction (as ratio of cortical area to total cross-sectional area (Ct.Ar/Tt.Ar).

Other characteristics

The following measurements were obtained for each participant at the time of the bone measurement (age) and at the closest index exam: height, weight, and estrogen use in women. Women were assigned to one of two “estrogenic status” groups: 1) premenopausal or postmenopausal on estrogen (estrogenrepleted) or 2) postmenopausal not on estrogen (estrogendepleted). Height (without shoes) was measured to the nearest one-fourth inch using a standard stadiometer. Weight (in light dress) was measured using a standardized balance-beam scale.

Statistical analysis

Descriptive statistics and analysis of correlations between the HR-pQCT indices and between them and DXA aBMD, height, and weight were performed using SAS (version 9.1.3, SAS Institute Inc., Cary, NC, USA). Variance component analyses (VCA) were

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performed using Sequential Oligogenic Linkage Analysis Routines version 2.0 (SOLAR[24]) to estimate heritability (h^2) of each trait, as the proportion of the total trait variance attributable to the additive effects of multiple genes (polygenic component) after removing variation owing to covariates. Wherever the trait's distribution was not normal, we performed normalization. Heritability estimates were calculated for vBMD and bone microarchitecture traits, adjusted for age, sex, and estrogenic status in women (Model 1). Two additional covariate models were tested: height and weight added to the Model 1 covariates (Model 2) and regional aBMD added to Model 2 (Model 3, radius only). Ultradistal aBMD measures were used in the analysis involving the radial microarchitecture traits (the distal-tibia aBMD was not available because it was not directly measured using the DXA scanner).

Phenotypic correlations were calculated among all pairs of microarchitecture traits in each bone and between the microarchitecture traits measured by HR-pQCT and radial aBMD by DXA. They were decomposed as follows. Bivariate VCA were performed for all pairs of microarchitecture traits in each bone and between the microarchitecture traits and regional aBMD for bone traits with significant heritability ($p < 0.05$). The phenotypic correlation coefficient (ρ_P) between any pair of traits was decomposed using the SOLAR version 2.0 as:

$$\rho_P = \rho_G \sqrt{h_1^2 h_2^2} + \rho_E \sqrt{(1 - h_1^2)(1 - h_2^2)} \quad (1)$$

where ρ_G and ρ_E represent the shared additive genetic and environmental influences, respectively, whereas $h_1^2 \text{and} h_2^2$ are the heritabilities of trait 1 and trait 2, respectively. SOLAR reports a significance of difference between estimated genetic correlation (ρ_G) and $\rho_G = 0$ (no genetic correlation), as well as $\rho_G = 1.0$ (absolute genetic correlation). For the studied traits, ρ_E would include all non-genetic factors similar between relatives, such as effects of household, diet, exercise, and other environmental factors influencing bone microarchitecture or dimensions. We calculated 95% confidence intervals of h^2 and phenotypic and genetic correlations empirically using non-parametric bootstrap samples. We used 200 bootstrap samples (generated by resampling pedigrees with replacement 200 times), calculated the h^2, ρ_P, and ρ_G for these bootstrap samples, and calculated the lower and upper 95% CIs as the 2.5 and 97.5 percentiles of the bootstrap distribution. More extensive details regarding the development, implementation, and power of bi- and multivariate extensions to heritability analyses have been published elsewhere.[25–27]

Results

Table 1 shows descriptive statistics of the study participants and their bone measurements. The average age of the 1064 Framingham subjects was 72.2 years; 57% were women, overwhelmingly (98.7%) postmenopausal. As shown in Table 2, estimates of heritability adjusted for age, sex, and estrogen status (Model 1) ranged from 0.193 (non-significant, trabecular number) to 0.828 ($p < 0.0001$, Ct.vBMD) in the radius and from 0.519 ($p < 0.0001$, trabecular thickness) to 0.983 ($p < 0.0001$, cortical cross-sectional area fraction, Ct.Ar/Tt.Ar) in the tibia. Further adjustment for height and weight generally attenuated h^2 of

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the traits (more at the radius, less profoundly at the tibia). Additional adjustment for the regional aBMD further decreased h^2 of the radial traits (except for radial Ct.Po and Tb.N, the heritabilities remained significant [$p \leq 0.01$]).

Having established the heritabilities for multiple HR-pQCT measures, we then tested for correlations between HR-pQCT and the anthropometric traits and UD aBMD. Most microarchitecture traits were positively correlated with height, except for radial Ct.vBMD ($R_{phenotypic} = -0.09$, $p = 0.004$), radial and tibial Ct.Ar/Tt.Ar (non-significant), and cortical porosity (also non-significant). There was a high phenotypic correlation between multivariable-adjusted total and trabecular vBMD at the radius and DXA-derived ultradistal aBMD (0.745 and 0.694, respectively), but only 0.397 for radial cortical vBMD (Table 3). In bivariate variance component analyses, there was a high genetic correlation between multivariable-adjusted total and trabecular vBMD at the radius and UD aBMD (0.811 and 0.917, respectively). Although these ρ_Gs were high, they were different from $\rho_G = 1.0$ (confidence interval for Tb.vBMD did include 1.0, whereas for Tt. vBMD was significantly lower than 1.0). Genetic correlations between radial cortical vBMD and UD aBMD were moderate, similar to their phenotypic correlations ($\rho_G = 0.505$). Environmental correlations of UD aBMD with the radial vBMD traits were generally less significant than corresponding ρ_Gs, ranging from 0.170 to 0.733 (Table 3). Moderate phenotypic correlations were found between ultradistal aBMD and radial cortical and trabecular traits (from 0.43 to 0.57), except for radial cortical porosity (Table 3).

Substantial genetic correlations were also found between radial total vBMD and the rest of the radial microarchitecture traits (ρ_G from 0.68 to 0.91, Table 4), except for cortical vBMD. (To note, because heritabilities of radial Ct.Po and Tb.N were non-significant, they were excluded from genetic correlations analysis). Likewise, high genetic correlations were observed between radial Ct.Ar/Tt.Ar and Ct.Th ($\rho_G = 0.901$) and between radial Tb.vBMD and Tb.Th ($\rho_G = 0.96$). At the tibia, a similar pattern of genetic correlations was observed between total vBMD and the rest of the microarchitecture traits, with ρ_Gs up to 0.95 (Table 5). Tibial cortical porosity had mostly negative or non-significant ρ_Gs with the rest of the microarchitecture traits, except for the expected high significant correlation observed for Ct.Po–Ct.vBMD pair ($\rho_G = -0.805$, $p = 0.0005$).

Environmental correlations among the microarchitecture traits were also substantial, with up to 0.96 ($p < 0.0001$) between radial Ct.Ar/Tt.Ar and Ct.Th; tibial ρ_Es were less significant, except for a pair Ct.Po–Ct.vBMD; this inverse correlation was highly significant ($\rho_G = -0.84$, $p = 0.0008$).

Discussion

Here we report data on the heritability estimates for bone mineral density and bone microstructure from a sample of older men and women from a population-based cohort, whose forearms and legs were measured using HR-pQCT to obtain measures of bone microarchitecture at the non-weight-bearing and weight-bearing bones, respectively. To date, studies of heritability of HR-pQCT measures have been limited by relatively small sample sizes, particularly in men.[11,16] Our study suggests that vBMD and bone microarchitecture

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indices measured by HR-pQCT are heritable. Estimates of the polygenic component of variance for these multiple traits adjusted for age and sex ranged from relatively low (19%) for radial trabecular number to very high (>90%) for tibial cortical dimensions. Heritabilities of height- and weight-adjusted trabecular vBMD were 62% (radius) and 56% (tibia). Of note, heritability estimate for height- and weight-adjusted ultradistal radius aBMD in the Framingham sample is 41.7%.

Our results were similar to those of Bjornerem and colleagues, who found that the proportion of variance accounted for by genetic factors ranged from 72% to 81% for the distal tibial total, cortical, and medullary cross-sectional area (CSA).[11] One explanation for such high heritability of lower-extremity traits may be related to the fact that lower-extremity bones are loaded with the full body weight during all upright non-sitting activities. To be able to sustain these forces, one has to have robust and well-structured bones; tibial cortical thickness and cross-sectional area capture the essence of bone's weight-bearing potential. Indeed, most microarchitecture traits positively correlate with height (see also Boutroy and colleagues[12] and Bjornerem and colleagues[28]), and the adjustment for height did, in general, decrease h^2, more at the radius, less profoundly at the tibia. The latter suggests that heritability of tibial "robustness" is mostly independent of a person's attained height.

One of the important findings from our data was that additional adjustment for radial aBMD, despite generally decreasing the heritability, did not fully eliminate it, which suggests that h^2 of bone microstructure is partly independent of DXA-derived aBMD. There were high phenotypic correlations between HR-pQCT-derived total and trabecular vBMD at the radius and UD aBMD (0.745 and 0.694, respectively); therefore, an adjustment for regional aBMD did indeed decrease heritability of the radial traits. This suggests that some of the phenotypic variance is shared between the radial microstructure traits and ultradistal-radius aBMD. The distal-tibia aBMD was not available because it was not directly measured by us with the DXA scanner, so we cannot make projections for the tibial microstructure.

A second novel aspect of our study was that we capitalized on the family-based nature of the Framingham study participants to determine if the genetic variance in compartment-specific vBMD is captured by conventional aBMD. High genetic correlations were found between regional areal BMD and total vBMD and trabecular vBMD of the radius (0.811 and 0.917, respectively), suggesting that there are common genetic factors that govern regional aBMD and (mostly trabecular) vBMD. Genetic correlations between cortical vBMD and the UD aBMD were moderate ($\rho_G = 0.505$), which may imply that the latter captures some unique aspects of bone architecture that aBMD does not. It is notable that the ρ_Gs between the aBMD and cortical and total vBMD were significantly lower than 1.0 (absolute sharing of heritability), which implies that there are unique factors for HR-pQCT-measured vBMD that are not captured by DXA aBMD.

One of the strengths of our study was the ability to answer the question of whether the genetic configurations of HR-pQCT traits are the same or different from the DXA-derived aBMD. High genetic correlations between measures suggest the possibility of a shared etiology, possibly at the molecular level. We have previously shown that genetic correlations

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among quantitative bone structure traits can predict how many associated variants are shared in GWAS between these traits.[14] Thus, unsurprisingly, high ρ_Gs were found between radial total vBMD and other microarchitecture traits (ρ_G up to 0.913 for cortical thickness), more so for the radius than the tibia. These high genetic correlations suggest that HR-pQCT-measured total vBMD is capturing most of the genetic variability in some microarchitecture indices between family members.

Unlike previous reports,[11,16] radial cortical porosity was not significantly heritable; because of this low h^2, its correlations with other bone traits were not decomposed. In contrast, tibial cortical porosity was heritable ($h^2 = 0.526$) and highly negatively correlated with Ct.vBMD ($\rho_G = -0.805$, $p = 0.0005$), which is expected because greater cortical porosity would result in lower volumetric cortical density.[11] Of note, directions of ρ_Gs between tibial cortical porosity and the rest of the microarchitecture traits were also negative. In the twin study by Bjornerem and colleagues, after additional adjustment of tibial porosity for total CSA, the estimate of the genetic component slightly decreased.[11] We similarly observed only a slight decrease while adjusting tibial cortical porosity for height and weight.

The design of this study does not allow discussing the exact mechanisms underlying the similarities or differences between the bone microstructural traits. Note that environmental correlations between the microarchitecture traits were also substantial, which points out the similar response to common environment by the various bone characteristics. Tibial ρ_Es were less significant than radial correlations, which conforms to our hypothesis of the dominance of early-life genetic programming on the weight-bearing tibia, which is less influenced by changing environment in the life course. Similarly to Bjornerem and colleagues,[11] we may conclude that genetic factors contribute to variability of HR-pQCT traits more than do environmental factors.

There were several limitations of our study. First, although our sample was substantial, with up to 1047 phenotyped participants, the sample size was still too modest to allow stratification by sex or by age. We recognize that there might be sex- and age-specific genetic signals on bone microarchitecture[29] (similar to the aBMD[30]), yet to be identified and validated. Second, we did not measure tibial aBMD, thus we cannot calculate genetic correlations between aBMD and HRpQCT measures at the tibia. Also, we acknowledge that although this first-generation HR-pQCT scanner provides unique measures of bone structure, the resolution limits the direct assessment of trabecular thickness and of smaller cortical pores. Although the accuracy of assessment of pores >140 μm is excellent,[31] the threshold-based cortical porosity measurement may have missed very small pores and therefore underestimated the absolute value of porosity. However, given the very strong association between threshold-based porosity measurements and those from synchrotron radiation micro-computed tomography ($r^2 = 0.94$), the heritability estimates would likely be the same had a density-based approach to assessment of cortical porosity or a higher-resolution in vivo imaging technique been used.

Importantly, our findings may be used to help inform other studies of the genetics of bone microarchitecture, which will need to narrow down the list of multiple measures generated

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by HR-pQCT to reduce the multiple testing penalty. One approach would be to focus on traits with heritabilities that are independent of aBMD. Also, knowledge of the shared heritability between the novel traits can serve to reduce the number of traits for genetic association studies. Thus, for example, very high genetic correlations, such as between cortical thickness and total vBMD or Ct.Ar/Tt.Ar (0.913 and 0.901, respectively) at the radius, would suggest that the analysis of these bone phenotypes will discover the same genetic variants;[14] therefore one might decide not to analyze both traits from such a pair. A note of caution should be sounded: One should not be fully guided by statistical tools, especially because the heritability estimate is sample-specific and depends on covariates included in the model.

In conclusion, our findings of high heritability of microarchitecture traits highlight the importance of further work to identify the specific variants underlying genetic susceptibility to volumetric bone density and fine structure of long bones, which holds promise of new mechanistic discoveries in etiology of bone fractures.

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Table 1

Sample Characteristics and Bone Measurements

Variable (unit)	*n*	Mean (or %)	SD
Age (years)	1064	72.2	7.7
Height (inches)	1063	65.4	3.7
Sex (men/women)	456/608	42.9/57.14%	
Postmenopausal women	600	98.7%	
Radial microarchitecture	986		
Total density, Tt.vBMD (mg/cm^3 HA)		311.53	68.96
Cortical porosity, Ct.Po (%)		3.96	2.20
Cortical thickness, Ct.Th (mm)		0.87	0.21
Cortical area fraction (Ct.Ar/TtAr) (%)		18.65	6.38
Cortical density, Ct.vBMD (mg/cm^3 HA)		957.04	60.40
Trabecular density, Tb.vBMD (mg/cm^3 HA)		163.34	43.35
Trabecular number, Tb.N (mm^{-1})		2.05	0.38
Trabecular thickness, Tb.Th (mm)		0.066	0.012
Tibial microarchitecture	1047		
Total density, Tt.vBMD (mg/cm^3 HA)		284.31	60.66
Cortical porosity, Ct.Po (%)		10.05	3.23
Cortical thickness, Ct.Th (mm)		1.19	0.30
Cortical area fraction (Ct.Ar/TtAr) (%)		15.24	5.38
Cortical density, Ct.vBMD (mg/cm^3 HA)		856.23	75.21
Trabecular density, Tb.vBMD (mg/cm^3 HA)		175.71	41.02
Trabecular number, Tb.N (mm^{-1})		2.08	0.40
Trabecular thickness, Tb.Th (mm)		0.070	0.012
DXA aBMD (g/cm^2)	1064		
Ultradistal radius		0.462	0.103

HA = hydroxyapatite.

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Table 2

Heritability (Estimate ± SE [95% Confidence Interval]) of Bone Microarchitecture and Density Traits

Trait	Model 1	Model 2	Model 3
Radial bone			
Ultradistal radius DXA aBMD	0.465 ± 0.117 [0.228, 0.729]	0.417 ± 0.117 [0.184, 0.624]	—
Total density (mg/cm^3 HA)	0.743 ± 0.117 [0.498, 0.949]	0.650 ± 0.123 [0.407, 0.880]	0.613 ± 0.125 [0.307, 0.823]
Cortical thickness (mm)	0.611 ± 0.117 [0.381, 0.875]	0.545 ± 0.129 [0.313, 0.743]	0.504 ± 0.140 [0.117, 0.719]
Cortical area fraction (Ct.Ar/Tt.Ar)	0.697 ± 0.119 [0.408, 0.881]	0.593 ± 0.127 [0.377, 0.816]	0.535 ± 0.132 [0.308, 0.825]
Cortical density (mg/cm^3 HA)	0.828 ± 0.135 [0.482, 1.000]	0.733 ± 0.142 [0.438, 0.998]	0.644 ± 0.152 [0.341, 0.929]
Cortical porosity (%)	0.278 ± 0.216 [0.0, 0.780]	0.244 ± 0.215 [0.0, 0.718]	0.227 ± 0.215 [0.0, 0.721]
Trabecular density (mg/cm^3 HA)	0.646 ± 0.142 [0.372, 0.903]	0.623 ± 0.143 [0.367, 0.897]	0.443 ± 0.151 [0.080, 0.690]
Trabecular number (mm^{-1})	0.193 ± 0.162 [0.0, 0.413]	0.184 ± 0.161 [0.0, 0.414]	0.082 ± 0.166 [0.0, 0.357]
Trabecular thickness (mm)	0.414 ± 0.160 [0.048, 0.749]	0.397 ± 0.160 [0.018, 0.715]	0.319 ± 0.153 [0.006, 0.615]
Tibial bone			
Total density (mg/cm^3 HA)	0.803 ± 0.108 [0.514, 1.000]	0.743 ± 0.114 [0.485, 1.000]	—
Cortical thickness (mm)	0.917 ± 0.110 [0.654, 1.000]	0.835 ± 0.121 [0.478, 0.998]	—
Cortical area fraction (Ct.Ar/Tt.Ar)	0.983 ± 0.097 [0.728, 1.000]	0.895 ± 0.108 [0.582, 1.000]	—
Cortical density (mg/cm^3 HA)	0.711±0.127 [0.392,0.931]	0.638±0.135 [0.353,0.878]	—
Cortical porosity (%)	0.526 ± 0.140 [0.270, 0.733	0.509 ± 0.142 [0.215, 0.709]	—
Trabecular density (mg/cm^3 HA)	0.554 ± 0.111 [0.430, 0.861]	0.561 ± 0.111 [0.325, 0.777]	—
Trabecular number (mm^{-1})	0.595±0.142 [0.302,0.879]	0.600±0.152 [0.274,0.893]	—
Trabecular thickness (mm)	0.519 ± 0.132 [0.225, 0.790]	0.480 ± 0.134 [0.202, 0.752]	—

Model 1: adjusted for sex and age and estrogenic status (women).
Model 2: Model 1 plus height and weight.
Model 3: Model 2 plus UD radial aBMD.

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Table 3

Correlations Between the Ultradistal Radial Bone Mineral Density Measured by DXA and HR-pQCT Parameters

DXA aBMD correlations with vBMD traits			
	Cortical density	**Trabecular density**	**Total density**
$R_{phenotypic}$ [95% confidence interval][a]	0.397 [0.345, 0.451]	0.694 [0.661, 0.727]	0.745 [0.716, 0.773]
ρ_G [95% confidence interval] (p zero; p 1.0)[b]	0.505 ± 0.167 [0.099, 0.801] ($p < 0.008$; $p =$ **0.0014**)	0.917 ± 0.091 [0.700, 1.000] ($p <$ **0.0005**; $p = 0.05$)	0.811 ± 0.094 [0.572, 0.990] ($p <$ **0.0005**; $p =$ **0.0012**)
ρ_E (p value)	0.170 ± 0.234 ($p > 0.05$)	0.572 ± 0.131 ($p = 0.014$)	0.733 ± 0.092 ($p <$ **0.001**)

Phenotypic correlations between DXA aBMD and microstructure traits				
Cortical porosity	Ct.Ar/TtAr	Cortical thickness	Trabecular number	Trabecular thickness
−0.09 [−0.16, −0.03]	0.54 [0.48, 0.59]	0.57 [0.53, 0.61]	0.43 [0.38, 0.48]	0.51 [0.46, 0.56]

[a] Partial correlations, adjusted for sex and age, estrogenic status, height, and weight.

[b] p value for difference from $\rho_G = 0$ and p value for difference from $\rho_G = 1.0$, respectively.

Bold indicates $p \leq 0.005$.

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Table 4

Genetic and Environmental Correlations for the Microarchitecture Traits (Radius)

	Total density	Ct.Ar/Tt.Ar	Cortical thickness	Cortical density	Trabecular density	Trabecular thickness
Total density (mg/cm^3 HA)	—	0.895 ± 0.049 (*p* < **0.0001**)	0.913 ± 0.066 (***p*** < **0.0001**)	0.227 ± 0.260 (*p* = 0.458)	0.791 ± 0.077 (***p*** < **0.0001**)	0.678 ± 0.136 (***p*** = **0.0037**)
Ct.Ar/Tt.Ar (ratio)	0.910 ± 0.031 (***p*** < **0.0001**)	—	0.901 ± 0.030 (***p*** < **0.0001**)	0.813 ± 0.072 (***p*** < **0.0001**)	0.479 ± 0.147 (*p* = **0.005**)	0.322 ± 0.207 (*p* = 0.168)
Cortical thickness (mm)	0.786 ± 0.060 (***p*** < **0.0001**)	0.962 ± 0.028 (***p*** < **0.0001**)	—	0.733 ± 0.093 (***p*** < **0.0001**)	0.380 ± 0.160 (*p* = 0.033)	0.209 ± 0.231 (*p* = 0.400)
Cortical density (mg/cm^3 HA)	0.763 ± 0.102 (***p*** < **0.0001**)	0.483 ± 0.214 (*p* = 0.171)	0.439 ± 0.211 (*p* = 0.158)	—	0.412 ± 0.188 (*p* = 0.015)	0.283 ± 0.218 (*p* = 0.198)
Trabecular density (mg/cm^3 HA)	0.793 ± 0.073 (***p*** < **0.0001**)	0.015 ± 0.237 (*p* = 0.951)	0.092 ± 0.220 (*p* = 0.685)	0.577 ± 0.293 (*p* = 0.034)	—	0.958 ± 0.070 (***p*** = **0.0001**)
Trabecular thickness (mm)	0.470 ± 0.157 (*p* = 0.037)	0.316 ± 0.181 (*p* = 0.114)	0.300 ± 0.174 (*p* = 0.109)	0.004 ± 0.248 (*p* = 0.985)	0.463 ± 0.161 (*p* = 0.083)	—

Genetic correlations (ρ_G) above the diagonal (*p* value for difference from $\rho_G = 0$); environmental correlations (ρ_E) below the diagonal. Adjusted for sex and age, estrogenic status, height, and weight. Bold indicates $p \leq 0.005$.

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Table 5

Genetic and Environmental Correlations for the Microarchitecture Traits (Tibia)

	Total density	Cortical porosity	Ct.Ar/Tt.Ar	Cortical thickness	Cortical density	Trabecular number	Trabecular density	Trabecular thickness
Total density (mg/cm^3 HA)	—	0.012 ± 0.233 (p = 0.960)	0.948 ± 0.190 (p = 0.059)	0.872 ± 0.148 (p = 0.053)	0.274 ± 0.233 (p = 0.337)	0.673 ± 0.174 (p = 0.015)	0.447 ± 0.186 (p = 0.121)	0.670 ± 0.118 (p < **0.001**)
Cortical porosity (%)	0.292 ± 0.164 (p = 0.126)	—	0.257 ± 0.141 (p = 0.099)	0.028 ± 0.158 (p = 0.859)	0.805 ± 0.065 (**p = 0.0005**)	0.035 ± 0.192 (p = 0.857)	0.117 ± 0.203 (p = 0.553)	0.138 ± 0.243 (p = 0.551)
Ct.Ar/Tt.Ar (ratio)	0.850 ± 0.033 (p < **0.001**)	0.367 ± 0.293 (p = 0.258)	—	0.930 ± 0.015 (p < **0.001**)	0.700 ± 0.073 (p < **0.001**)	0.011 ± 0.186 (p = 0.951)	0.212 ± 0.121 (p = 0.106)	0.397 ± 0.154 (p = 0.014)
Cortical thickness (mm)	0.745 ± 0.053 (**p < 0.0001**)	0.444 ± 0.299 (p = 0.138)	0.919 ± 0.081 (p = 0.201)	—	0.480 ± 0.103 (**p = 0.002**)	0.086 ± 0.140 (p = 0.552)	0.164 = 0.136 (p = 0.256)	0.268 = 0.163 (p = 0.110)
Cortical density (mg/cm^3 HA)	0.693 ± 0.098 (**p < 0.0001**)	0.835 ± 0.071 (p = **0.0008**)	0.660 ± 0.217 (p = 0.119)	0.736 ± 0.225 (p = 0.048)	—	0.267 ± 0.158 (p = 0.105)	0.376 ± 0.172 (p = 0.031)	0.265 ± 0.210 (p = 0.186)
Trabecular number (mm^{-1})	0.386 ± 0.113 (p = 0.014)	0.129 ± 0.206 (p = 0.540)	0.494 ± 0.319 (p = 0.145)	0.670 ± 0.413 (p = 0.089)	0.048 ± 0.253 (p = 0.847)	—	0.639 ± 0.101 (**p = 0.002**)	0.023 ± 0.187 (p = 0.900)
Trabecular density (mg/cm^3 HA)	0.704 ± 0.067 (**p = 0.0001**)	0.325 ± 0.194 (p = 0.104)	0.861 ± 0.507 (p = 0.045)	0.625 ± 0.337 (p = 0.074)	0.178 ± 0.232 (p = 0.428)	0.583 ± 0.134 (p = 0.013)	—	0.721 ± 0.094 (p < **0.001**)
Trabecular thickness (mm)	0.394 ± 0.187 (p = 0.112)	0.328 ± 0.168 (p = 0.063)	0.011 ± 0.288 (p = 0.970)	0.063 ± 0.258 (p = 0.808)	0.242 ± 0.199 (p = 0.224)	0.335 ± 0.199 (p = 0.105)	0.656 ± 0.117 (**p = 0.004**)	—

Genetic correlations (ρ_G) above the diagonal (p value for difference from ρ_G=0); environmental correlations (ρ_E) below the diagonal. Adjusted for sex and age, estrogenic status, height, and weight. Bold indicates $p \leq 0.005$.

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