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Familial resemblance in trabecular and cortical volumetric bone mineral density and bone microarchitecture as measured by HRpQCT

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ABSTRACT

To estimate the heritability of bone geometry, volumetric bone mineral density (vBMD) and microarchitecture of trabecular (Tb) and cortical (Ct) bone measured by high resolution peripheral quantitative computerised tomography (HRpQCT) at the distal radius and tibia and to investigate the genetic correlations of these measures.
Participants were 177 mother-offspring pairs from 162 families (mothers, mean age (SD) = 52.1 (4.7) years; offspring, 25.6 (0.73) years). Trabecular and cortical bone measures were obtained by HRpQCT. Multivariable linear regression was used to analyse the association of bone measures between mother and offspring. Sequential Oligogenic Linkage Analysis Routines (SOLAR) software was utilised to conduct quantitative genetic analyses.
All maternal bone measures were independently associated with the corresponding bone measures in the offspring before and after adjustment for age, sex, weight and height. Heritability estimates ranged from 24% to 67% at the radius and from 42% to 74% at the tibia. The relationship for most bone geometry measures was significantly stronger in mother-son pairs ($n = 107$) compared with mother-daughter pairs ($n = 70$) ($p < 0.05$). In contrast, the heritability for most vBMD and microarchitecture measures were higher in mother-daughter pairs. Bivariate analyses found moderate to strong genetic correlations across all measures between radius and tibia ($R_g = 0.49$ to 0.93).
Genetic factors have an important role in the development of bone geometry, vBMD and microarchitecture. These factors are strongly shared for the radius and tibia but vary by sex implying a role for imprinting.

1. Introduction

Osteoporosis is a major public health issue resulting in a substantial societal and individual burden [1]. This disease is characterized by low bone mineral density (BMD) and microarchitectural deterioration, resulting in an increased risk of fractures [2]. Areal bone mineral density (aBMD) measured by dual energy x-ray absorptiometry (DXA) is generally considered as the gold standard for diagnosis of osteoporosis [3]. DXA has also been widely used for determination of fracture risk and adopted in many fracture risk assessment tools, such as Fracture Risk Assessment Tool (FRAX) [4]. However, both BMD and bone microarchitecture contribute to fracture risk and these cannot be fully assessed by aBMD. Indeed, most fractures occur in people classified as osteopenic on aBMD [5], highlighting the potential importance of including bone volumetric bone mineral density (vBMD) and bone microarchitecture in estimating fracture risk.

In addition to environmental factors, genetic factors play an important role in determining fracture risk [6]. The role of genetics in aBMD has been well-defined, with 41% to 85% of variation in aBMD being attributable to genetic factors depending on skeletal site and age [7–9]. Our previous study showed sex differences in the heritability of aBMD in prepubertal children [10]. Recent genome wide association studies (GWAS) have identified >60 genes/loci linked with aBMD [11]. However, there are few studies reporting the heritability of vBMD and microarchitecture, and these are in middle-aged female twins or older families [12–14]. No study has been conducted in early adulthood, around the time that peak bone mass (PBM) is attained.

Therefore, the aim of this study is to estimate the heritability for bone geometry, vBMD and bone microarchitecture measures at the distal radius and tibia and to investigate the genetic correlations of these measures in mother-offspring pairs when the offspring are young adults (aged 25 years).

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Table 1
Participants bone measurements by StrAx 1.0.

	Mothers ($n = 162$)	Sons ($n = 107$)	Daughters ($n = 70$)
Radius			
Geometry			
Tt.Ar (mm^2)	224.1 (33.8)	307.7 (63.6)	221.2 (42.1)**
Ct.Ar (mm^2)	91.0 (9.2)	115.7 (15.1)	88.8 (11.2)**
Ma.Ar (mm^2)	133.1 (28.2)	192.0 (54.0)	132.4 (34.7)**
Volumetric density			
Tt.vBMD (mg HA/cm^3)	419.5 (75.6)	433.5 (70.4)	415.7 (69.2)
Ct.vBMD (mg HA/cm^3)	821.2 (78.6)	803.4 (62.6)	802.8 (75.4)
Tb.vBMD (mg HA/cm^3)	135.8 (50.9)	199.0 (46.7)	145.0 (41.8)**
Microarchitecture			
Ct.Th (mm)	1.89 (0.18)	2.07 (0.26)	1.82 (0.18)**
Total cortical porosity (%)	47.50 (6.20)	49.13 (4.99)	48.94 (6.06)
Compact cortical porosity (%)	30.59 (5.49)	34.94 (4.16)	32.02 (5.30)
Outer TZ porosity (%)	33.77 (4.26)	37.19 (3.24)	35.53 (4.13)
Inner TZ porosity (%)	81.62 (3.52)	79.33 (3.37)	82.16 (2.99)
Tb.N (mm^{-1})	3.32 (0.55)	3.78 (0.42)	3.45 (0.46)**
Tb.Th (mm)	0.18 (0.01)	0.19 (0.01)	0.18 (0.01)**
Tb.Sp (mm)	1.12 (0.25)	0.88 (0.19)	1.05 (0.23)**
Tb.BV/TV (%)	4.39 (2.13)	7.30 (2.30)	4.46 (1.65)**
Tibia			
Geometry			
Tt.Ar (mm^2)	607.8 (97.5)	790.5 (160.3)	594.9 (104.3)**
Ct.Ar (mm^2)	197.3 (19.7)	246.5 (28.2)	199.1 (20.4)**
Ma.Ar (mm^2)	410.5 (87.0)	544.0 (145.7)	395.8 (97.0)**
Volumetric density			
Tt.vBMD (mg HA/cm^3)	336.7 (59.7)	385.3 (57.5)	371.9 (64.0)
Ct.vBMD (mg HA/cm^3)	722.2 (74.5)	758.3 (54.7)	754.1 (71.0)
Tb.vBMD (mg HA/cm^3)	144.2 (41.2)	206.9 (39.9)	169.6 (41.1)*
Microarchitecture			
Ct.Th (mm)	2.30 (0.22)	2.51 (0.28)	2.35 (0.27)*
Total cortical porosity (%)	55.12 (5.83)	52.44 (4.32)	52.59 (5.59)
Compact cortical porosity (%)	36.48 (6.62)	35.03 (4.31)	33.42 (5.80)
Outer TZ porosity (%)	37.84 (5.50)	36.68 (3.24)	35.94 (4.22)
Inner TZ porosity (%)	81.99 (3.11)	78.41 (2.91)	80.17 (3.19)
Tb.N (mm^{-1})	3.43 (0.57)	3.95 (0.47)	3.71 (0.53)*
Tb.Th (mm)	0.18 (0.01)	0.190 (0.01)	0.185 (0.01)**
Tb.Sp (mm)	1.11 (0.23)	0.88 (0.15)	0.99 (0.19)**
Tb.BV/TV (%)	5.57 (1.85)	8.81 (2.04)	6.75 (1.95)**

Values are mean (standard deviation). Tt.Ar, total cross sectional area; Ct.Ar, total cortical area; Ma.Ar, Medullary area; TZ: transitional zone; Tt.vBMD, total volumetric bone density; Ct.vBMD, total cortical volumetric bone density; Tb.vBMD, trabecular volumetric bone density; Ct.Th, total cortical thickness; Tb.N, trabecular number; Tb.Th, trabecular thickness; Tb.Sp, trabecular separation; Tb.BV/TV, trabecular bone volume fraction. HA: hydroxyapatite.
** $p < 0.001$.
* $p < 0.01$ for comparison of means by sex, all other comparisons are not significant.

2. Materials and methods

2.1. Participants

T-Bone is a cohort study taken from within a Tasmanian birth cohort from 1988 and 1989. Over this time, there were 13,592 live births in Tasmania. At the time of these births, a scoring system was used to select infants at higher risk of Sudden Infant Death Syndrome (SIDS) for possible participation in an infant health study [15]. From these, 1500 infants who were born in Southern Tasmania were enrolled in the current study. After 8 years, 890 of these 1500 participants and their mothers were assessed in 1996 ($n = 444$) and 1997 ($n = 446$). We also measured 415/1500 (28.9%) participants in 2004–2005 when offspring were 16 years old. These 415 participants with their mothers were invited again to participate in a further study in 2013–2015. This study was granted approval by the University of Tasmania Ethics Committee (human experimentation). All participants and their mothers both provided written informed agreement. This is a cross-sectional analysis of data from mothers and offspring when offspring were aged 25 years.

2.2. Bone microarchitecture measurement

High-Resolution Peripheral Quantitative Computed Tomography (Xtreme CT, Scanco Medical, Brüttisellen, Switzerland) was used to scan the non-dominant distal tibia and radius in both mother and offspring. In the case of the previous fracture at either of these sites, the contralateral limb was scanned. Region of interest of 9.02 mm (110 CT slices) were at the standardised distance of 22.5 mm and 9.5 mm from the manually positioned reference line at the end plate of the distal tibia and radius respectively. Both the default Scanco analysis [16] and StrAx 1.0 were used to analysis the scans. StrAx1.0 is a non-threshold-based segmentation algorithm (StraxCorp Pty Ltd., Melbourne, Australia) [17] and its accuracy, reproducibility and the segmentation algorithm are fully described in the patent [18]. StrAx1.0 is designed to analyse images automatically and the assessment of image quality is programmed in the software. The image quality is usually compromised by three problems: 1. motion during the scan; 2. ring artifact; 3. image reconstruction error. The software would reject the image from analysis if any of these three problems are detected. StrAx1.0 analysis uses an algorithm that separates bone from background (soft tissue) and bone into its compact-appearing cortex, the fragmented cortex forming an outer and inner transitional zone and the trabecular compartment. From the segmented image, porosity is quantified as the proportion of voxels within the cortical compartment that contain void which fully described in previous paper [17]. The 40 most proximal slices were chosen because the thicker cortex allows accurate assessment of porosity. Total, cortical, and medullary cross sectional area of

Table 2
Participants' characteristics and bone measurements by Scanco.

	Mothers ($n = 162$)	Sons ($n = 107$)	Daughters ($n = 70$)
Age	52.1 (4.7)	25.5 (0.8)	25.6 (0.7)
Height (cm)	161.8 (5.9)	177.5 (6.0)	163.7 (7.0)**
Weight (kg)	72.8 (16.9)	83.3 (15.2)	73.3 (18.6)**
Radius			
Geometry			
Tt.Ar (mm^2)	258.7 (37.7)	351.0 (69.3)	253.1 (45.9)**
Ct.Ar (mm^2)	57.6 (10.7)	73.0 (13.7)	55.3 (10.6)**
Tb.Ar (mm^2)	196.5 (37.7)	272.9 (69.2)	193.7 (45.7)**
Volumetric density			
Tt.vBMD (mg HA/cm^3)	349.7 (62.0)	367.7 (58.9)	348.5 (58.3)*
Ct vBMD (mg HA/cm^3)	895.5 (49.5)	867.9 (58.4)	885.4 (49.9)*
Tb vBMD (mg HA/cm^3)	170.9 (38.5)	217.5 (37.3)	176.3 (33.2)**
Microarchitecture			
Ct.Th (mm)	0.84 (0.17)	0.91 (0.19)	0.84 (0.17)*
Tb.N (mm^{-1})	2.12 (0.32)	2.36 (0.25)	2.18 (0.27)**
Tb.Th (mm)	0.07 (0.01)	0.08 (0.01)	0.07 (0.01)**
Tb.Sp (mm)	0.42 (0.14)	0.35 (0.06)	0.40 (0.07)**
Tibia			
Geometry			
Tt.Ar (mm^2)	647.8 (1.4)	841.8 (165.6)	629.7 (109.7)**
Ct.Ar (mm^2)	112.2 (20.0)	152.4 (26.2)	121.0 (20.8)**
Tb.Ar (mm^2)	530.8 (103.0)	687.8 (167.1)	506.5 (115.2)**
Volumetric density			
Tt.vBMD (mg HA/cm^3)	305.6 (51.7)	350.5 (50.9)	339.2 (56.6)
Tb.vBMD (mg HA/cm^3)	174.2 (35.0)	224.9 (34.5)	195.5 (34.8)**
Ct.vBMD (mg HA/cm^3)	876.8 (51.0)	884.3 (32.1)	901.4 (39.6)*
Microarchitecture			
Ct.Th (mm)	1.13 (0.23)	1.34 (0.28)	1.25 (0.25)*
Tb.N (mm^{-1})	2.01 (0.35)	2.28 (0.30)	2.12 (0.33)*
Tb.Th (mm)	0.07 (0.01)	0.08 (0.01)	0.08 (0.01)**
Tb.Sp (mm)	0.44 (0.13)	0.36 (0.06)	0.41 (0.08)**

Values are mean (standard deviation). Tt.Ar, total cross sectional area; Ct.Ar, total cortical area; Tb.Ar, total trabecular area; Tt.vBMD, total volumetric bone density; Ct.vBMD, total cortical volumetric bone density; Tb.vBMD, trabecular volumetric bone density; Ct.Th, cortical thickness; Tb.N, trabecular number; Tb.Th, trabecular thickness; Tb.Sp, trabecular separation; HA:hydroxyapatite.
** $p < 0.001$.
* $p < 0.05$ for comparison of means by sex, all other comparisons are not significant.