

Original Article

**Fracture Risk and Height: an Association Partly Accounted for by Cortical Porosity of Relatively Thinner Cortices<sup>†</sup>**

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**Short title:** Height, Cortical Porosity and Fracture risk

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**Abstract**

Taller women are at increased risk for fracture despite having wider bones that better tolerate bending. As wider bones require less material to achieve a given bending strength, we hypothesized that taller women assemble bones with relatively thinner and more porous cortices because excavation of a larger medullary canal may be accompanied by excavation of more intracortical canals. Three-dimensional images of distal tibia, fibula and radius were obtained *in vivo* using high-resolution peripheral quantitative computed tomography in a twin study of 345 females aged 40 to 61 years, 93 with at least one fracture. Cortical porosity below as well as above 100 microns, and microarchitecture were quantified using Strax1.0, a new algorithm. Multivariable linear and logistic regression using generalized estimating equation methods quantified associations between height and microarchitecture and estimated the associations with fracture risk. Each standard deviation (SD) greater height was associated with a 0.69 SD larger tibia total cross sectional area (CSA), 0.66 SD larger medullary CSA, 0.50 SD higher medullary CSA/total CSA (i.e., thinner cortices relative to the total CSA due to a proportionally larger medullary area) and 0.42 SD higher porosity (all  $p < 0.001$ ). Cortical area was 0.45 SD larger in absolute terms but 0.50 SD smaller in relative terms. These observations were confirmed by examining trait correlations in twin pairs. Fracture risk was associated with height, total CSA, medullary CSA/total CSA and porosity in univariate analyses. In multivariable analyses, distal tibia, medullary CSA/total CSA and porosity predicted fracture independently; height was no longer significant. Each SD greater porosity was associated with fracture; odds ratios; distal tibia 1.55; 95% CI: 1.11-2.15, distal fibula 1.47; 95% CI 1.14-1.88, distal radius 1.22; 95% CI 0.96-1.55. Taller women assemble wider bones with relatively thinner and more porous cortices predisposing to fracture.

**Key words:** cortical porosity, cortical thickness, fracture risk, height, high-resolution peripheral quantitative computed tomography.

## Introduction

Taller persons are at increased risk for hip, non-vertebral and vertebral fractures.<sup>(1-6)</sup> Although well documented, this liability to fracture is counter-intuitive because taller persons assemble longer and wider bones with more mass.<sup>(7)</sup> Greater bone width and greater bulk confer resistance to bending and greater load bearing capacity.<sup>(8)</sup> However, these advantages may be offset by the imperative to minimize bulk during assembly of a larger skeleton because bulk takes time to grow, is costly to maintain and limits mobility.<sup>(9)</sup>

Bulk is minimized by taking advantage of the effect of geometry on bone strength.<sup>(7)</sup> For example, during growth, periosteal apposition enlarges the diameter of a long bone as it increases in length. Concurrently, endocortical resorption excavates the medullary cavity lessening the net increase in cortical thickness produced by periosteal apposition but also producing an outward shift of the cortical bone which increases resistance to bending to the fourth power of its radius.<sup>(10)</sup> This disproportionate increase in resistance to bending allows a wider bone to be assembled using less mass relative to its size - the cortex is thicker in absolute terms but thinner *relative* to its diameter.<sup>(7,9,11)</sup> Compressive strength is not compromised because the relatively thinner cortex is distributed around a larger perimeter so cortical area is not reduced.

Mass is minimized in another way. Cortical bone is not 'compact'.<sup>(12)</sup> In young adults, 70% of the cortical volume contained within the periosteal and endocortical surfaces is mineralized bone matrix volume and 30% consists of Haversian and Volkmann canals 'seen' as porosity in cross section.<sup>(13,14)</sup> The surfaces of these canals are contiguous with the endocortical surface of the medullary canal.<sup>(15)</sup> Bone modelling and remodelling occur upon these surfaces;<sup>(16)</sup> greater excavation upon the endocortical surface enlarges the medullary canal volume in taller persons and may be accompanied

by correspondingly greater intracortical remodelling forming more osteons, each with a central Haversian canal of an intracortical canal system which in cross section appears as pores.

Thus, in taller women, distributing a relatively thinner cortex radially optimizes bone's ability to tolerate bending and minimizes the mass needed to do so. While advantageous in young adulthood, the precarious balance between strength and lightness may become a liability after menopause when remodelling accelerates and becomes unbalanced;<sup>(17)</sup> more bone is removed than replaced; trabeculae thin, disappear and become disconnected and cortices thin and become porous. We hypothesized that accelerated and unbalanced remodelling compromises the skeleton of taller women more greatly because they assemble their skeleton with relatively thinner and more porous cortices, structures that are more liable to becoming fragile when bone loss occurs and more liable to fracture following a fall.

## **Methods**

### **Participants and procedures**

We studied 113 monozygotic (MZ) and 72 dizygotic (DZ) healthy Caucasian female twin pairs and 5 singletons (their sisters did not attend) aged 40-61 years in Melbourne, Australia in 2008-2009.<sup>(18)</sup> We excluded 30 women using hormone replacement therapy. Of the 345 women remaining, 212 (61.5%) were premenopausal (a regular cycle in the last 3 months), 42 (12.2%) were perimenopausal (no cycles for 3-12 months), and 91 (26.4%) were postmenopausal (amenorrhea for > 1 year). Ninety-three women had a history of fracture occurring during childhood or adulthood. Fractures were reported at the wrist (n = 24), arm (n = 21), hand (n = 4), elbow (n = 1), shoulder (n = 3), ankle (n = 11), lower leg (n = 4), foot (n = 5), femur (n = 3), clavicle (n = 7), rib (n = 6), vertebrae, sacrum, coccyx and sternum (n = 1 each). Of these fractures, 46 occurred before participants were 16 years of age. The fracture history was carefully documented during an interview. After exclusion of bone scans with movement artefacts, we had valid measurements at the distal tibia, fibula, and radius in 324, 321

and 313 women, respectively. All women gave written informed consent. The study was approved by The Austin Health Ethics Committee.

### **Bone microarchitecture**

High-resolution 3-dimensional peripheral quantitative computed tomography (HR-pQCT, XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland, isotropic resolution of 82  $\mu\text{m}$ ) was used to obtain images at the non-dominant distal tibia, fibula and radius.<sup>(19)</sup> The 110 CT slices were obtained in a standardized distance of 22.5 and 9.5 mm from a reference line that was manually placed at the endplate of the distal tibia and radius, respectively.<sup>(20)</sup>

Cortical porosity, the total, cortical and trabecular cross sectional areas (CSAs) and volumetric bone mineral density (vBMD) were quantified using StrAx1.0, a new non-threshold based method for quantifying porosity *in vivo*.<sup>(21,22)</sup> The 40 most proximal slices in the 110 slices region of interest were chosen because the cortex is thicker allowing assessment of porosity accurately. The 70 more distal slices include thinner, sometimes trabecularized cortices that are not suitable for quantification of porosity.

To quantify porosity, first, bone is automatically segmented from the surrounding soft tissue and then into its compartments using curve profile analysis.<sup>(21)</sup> Cortical porosity is quantified by estimating the void fraction of each voxel. To do so, first, the mineralized bone matrix volume of each voxel is quantified using an interpolation function derived from the attenuation of voxels containing fully mineralized bone matrix which has a density of 1200mgHA/c and is assigned a value of 100%. Voxels that are completely empty and have an attenuation equivalent to background are assigned a value of 0%. The volume fraction of a voxel that is void (i.e., porosity) is 100% minus the mineralized bone matrix fraction.

Osteoid, once deposited, is mineralized and so becomes 'bone'. Bone matrix reaches 80% of its maximum (1200 mgHA/cc) within 2-3 days. Only ~ 0.5% of cortical volume is osteoid at any time.<sup>(23)</sup>

Thus, at a resolution of ~ 82 microns, voxels with attenuation of 80% of the maximum attenuation produced by 1200 mg HA/cc or below, must have a pore or part of a pore due to the presence of a Haversian canal as these pores are on average 50 microns diameters<sup>(24)</sup> or a resorption cavity of 50-150 microns depending on its stage of remodeling. Any voxels with attenuation between 80-100% of the maximum are unlikely to contain Haversian canals (few Haversian canals are less than 25 microns diameter). They most likely contain almost exclusively younger newly deposited bone producing the heterogeneity in mineralization that could be mistakenly interpreted as porosity and so these voxels are excluded in calculating porosity; any variance in porosity is therefore not due to variance in mineralization.

The porosity is calculated in the remaining voxels presented as the average void volume fraction of all voxels, not only the empty voxels, but also the partly empty voxels for the whole cortical compartment. In brief, porosity is quantified in the compact-appearing and the transitional or cortico-trabecular zone. Distal tibia porosity of the compact-appearing cortex is ~30% that of the outer and inner transitional zones are ~40% and ~80%. This gives an average or net porosity of 57.4% for the total cortex (compact-appearing plus transitional zones, Table 1). Porosity is higher than previously reported because the Strax software quantifies porosity below as well as above 100 micron.<sup>(21,22)</sup> Previous methods quantify porosity of the compact-appearing cortex only, and quantify porosity over 100 microns only even though 80% of cortical porosity is under 100 microns.

Segmentation and quantification of porosity is accurate with  $R^2$  ranging from 0.88 to 0.99 at the distal radius and tibia assessed *ex vivo* compared to gold standard micro-CT (19 micron resolution).

Differences between porosity measured using the gold standard and porosity measured using StrAx software in HRpQCT images did not exceed 5%.<sup>(22)</sup> The method is also reproducible with root mean square error of the coefficient of variation between 0.54 to 3.0%.<sup>(21,22)</sup>

We used the ratio medullary CSA/total CSA as a measure of relative cortical thickness because cortical thickness varies around the perimeter of bones and along the bone length such that thicknesses are not normally distributed. Median cortical thickness is a better prediction of cortical area and strength than the mean.<sup>(25)</sup> A larger medullary area relative to the total CSA reflects greater excavation upon the endocortical surfaces relative to periosteal apposition which enlarges the medullary canal volume while producing a smaller cortical area *relative* to the total bone area, and so a thinner cortex relative to the total CSA of the in wider bones.<sup>(11)</sup> Daily quality control was carried out by scanning a phantom containing rods of hydroxyapatite (QRM Moehrendorf, Germany). The exposure dose of radiation exposure was ~5  $\mu$ Sv per measurement at each of the distal tibia and radius sites. Height and weight were measured in light clothing without shoes.

### **Statistical analyses**

Summary statistics are presented as mean and standard deviation (SD). Missing values were imputed for the multivariable analysis using random forest method. All variables were standardised to have mean zero and standard deviation of one. The generalized estimating equation (GEE) method was used to compare mean difference between women with and without fractures. It also used to assess the relationship between height as predictor and each of microarchitecture variables as outcomes, adjusted for age and weight. This method takes into account within twin pair correlations, which is needed when twins are analysed as individuals, because the sisters are not independent participants. We used the same method to assess the relationship between total CSA as predictor and other microarchitecture variables. Within twin pair differences (the difference in a same trait between twins), were analysed

for MZ and DZ twin pairs. Simple linear regression without intercept parameter was used to assess relationships between within twin pair differences in porosity and within twin pair differences in height, total CSA, medullary CSA and medullary CSA/total CSA.<sup>(26,27)</sup>

Logistic regression models were used to examine the association between height and bone structure and fracture risk. Again, we used the GEE method for estimation. Nonparametric regression analyses identified that the relationship height and fracture risk was quadratic for majority of the data. Note that nonparametric regression does not provide ORs or identify outliers. We examined the data fitting a parametric regression model using a quadratic function for height. This identified 9 outliers, women without fractures with height over 175 cm. These outliers were influential data points that distorted the estimated regression coefficients.<sup>(28)</sup> These subjects were excluded from logistic regression analyses because they were not consistent with the quadratic relationship of height on fracture risk seen in most of data (n = 316). Inclusion of these outliers did not change the association between height and bone structure, or between bone structure and fracture risk.

The chi-square statistic was used to determine significance of predictors. Predictors with p-value less than 0.15 from the univariate analyses were included in the multivariable logistic regression models and the final model was selected using the stepwise regression method with variables retained in the final model if p-value less than 0.05. All analyses were performed using public available R package.<sup>(29)</sup>

Within R package we used package ‘geepack’ for GEE method, ‘sm’ and for nonparametric smoothing and “missForest” for imputation.<sup>(30-32)</sup>

## **Results**

### **Height, bone size and bone microarchitecture**

The women had a mean age of 49.0 years (SD = 5.3; range 40.3-61.3), height 163.1 cm (SD = 6.3; range 150-187), weight 69.9 kg (SD = 14.9, range 40.8-120.3). Mean and SD for the microstructural



features at the three sites are given in Table 1. Height and total CSA were associated with each microarchitectural trait at each of the three sites (all  $p < 0.001$ , except for trabecular vBMD, Table 1). A SD greater height (6.3 cm) was associated with a 0.69 SD larger tibia total CSA. Greater height and total tibia CSA were each associated with a larger cortical and medullary CSA and a larger medullary CSA/total CSA (and a lower cortical CSA/total CSA), so taller women had relatively thinner cortices.

Taller women also had lower tibia total vBMD due to the relatively larger medullary CSA producing a relatively thinner cortex, and lower cortical vBMD produced by more porous cortices. Trabecular vBMD was not lower in taller women. A SD greater height was associated with a 0.42 SD higher tibia porosity, and a SD larger tibia total CSA was associated with a 0.65 SD higher porosity. Fig. 1 shows several of these relationships and the correlation between cortical thickness (medullary CSA/total CSA) and cortical porosity at the distal tibia. Plots for the distal fibula and radius were similar (not shown).

Within twin pair differences showed that a 1 SD larger differences in height, distal tibia total CSA, medullary CSA and medullary CSA/total CSA was associated with a larger within twin differences in porosity of 1.8%, 3.1%, 3.4% and 1.5%, respectively (all  $p < 0.001$ , Fig. 2). Similar associations were observed at distal fibula and distal radius (not shown).

### **Height, bone structure and fracture risk**

The mean age of first fracture was 22.7 years (range 2-58), and the mean time since first fracture was 28 years (range 1-52) for the 93 women with fracture. In pre-, peri- and postmenopausal women, 44 of 212 (20.8%), 18 of 42 (42.9%) and 31 of 91 (34.1%) women reported a fracture. The differences between fracture and non-fracture groups are shown in Table 2. In univariate logistic regression analyses, age, height, distal tibial total bone CSA, medullary CSA/total CSA (a surrogate of cortical

thickness) and cortical porosity were associated with fracture (Table 3). Cortical porosity of distal fibula, was also associated with fracture as was cortical vBMD (the inverse of porosity) but this did not reach significance at the distal radius. In multivariable logistic regression analyses, at the distal tibia, higher cortical porosity and a larger medullary CSA/total CSA remained independently associated with fracture in the final model (Table 3). The independent and non-linear effects of the larger medullary CSA/total CSA and higher porosity on the fracture probability are also shown in Fig. 3. Height had independent effects on fracture risk before, but not after, taking tibial medullary CSA/total CSA into account. Similarly the total CSA (bone width) had independent effects on fracture risk before, but not after, taking tibial medullary CSA/total CSA into account. Cortical thickness, correlated inversely with medullary CSA/total CSA ( $r = -0.88$ ) and when expressed as a quadratic term the odds ratio (OR) for fracture was 1.30; 95% CI 1.09-1.57,  $p = 0.004$ , similar to that observed with medullary CSA/total CSA, 1.37; 95% CI 1.17-1.61,  $p < 0.001$ .

Each SD higher cortical porosity was associated with a higher OR for fracture at the distal tibia of 1.55; 95% CI: 1.11-2.15 and at the distal fibula of OR = 1.47; 95% CI 1.14-1.88. At the distal radius, porosity was associated with fracture, but not significantly; OR = 1.22; 95% CI 0.96-1.55, while height and trabecular vBMD were independently associated with fracture. Weight was not associated with fracture (OR = 1.06; 95% CI 0.80-1.39). Nor was tissue mineralization density associated with fracture. Adjustment for weight did not change the results. In addition, adjustment for the mineralization levels did not change the results.

## Discussion

The association between height and increased fracture risk,<sup>(1-6)</sup> particularly hip and other non-vertebral fractures, is reported to be due to the greater loads imposed upon bone during a fall, a larger hip axis length and longer moment arms.<sup>(33-36)</sup> We report the increased fracture risk is also due to taller women

having their longer and wider bone assembled with a relatively thinner cortex (relative to its cross sectional area), and a cortex that was more porous. Analysis of co-twin pair differences was confirmatory; the taller twin had a wider bone with relatively thinner and more porous cortices.

The higher fracture risk is likely to be due to two factors, the assembly of a skeleton during growth that is more prone to becoming fragile with loss of bone during aging. At the completion of growth, taller women assemble a larger but relatively lighter skeleton; their longer and wider bones have a lower peak volumetric density because excavation of a larger medullary cavity relative to the total cross sectional area results in a cortex that is thinner relative to this larger total cross sectional area.

The relatively thinner cortex is also more porous. The work confirm the study by Jepsen et al. who reported greater total CSA was associated with higher porosity.<sup>(11)</sup> They also reported wider bones had a lower tissue mineral density while more slender bones were assembled with lower porosity and higher tissue mineral density.

Growth minimizes bulk by resorptive excavation of a larger medullary cavity and resorptive excavation of more osteons, each with their central Haversian canals. These canals form the porosity seen in cross sections and most are under 100 microns in diameter. This relatively thinner and more porous cortex is shifted radially conferring greater resistance to bending.<sup>(9,37)</sup> Finding that many of these fractures occurred during childhood and 30% were recurrent suggests the greater porosity may be established during growth.

Thus, taller women have relatively smaller mineralized bone matrix volume and larger void volume within a relatively thinner cortex. This structural design, while achieving strength and lightness at completion of growth, may become a liability because it is likely to be more susceptible to becoming

fragile after menopause when remodelling intensity increases and the negative bone balance worsens.<sup>(18)</sup> Higher remodelling upon the more numerous Haversian canals, and the larger endocortical surface, removes more mineralized bone matrix volume from a skeleton that has relatively less mineralized bone matrix volume to lose. More bone is lost from an ever decreasing volume of bone. Haversian canals enlarge focally, coalesce forming large pores which fragment the relatively thinner cortex.<sup>(12)</sup>

Porosity increases fracture risk because the stiffness of cortical bone is proportional to the 7<sup>th</sup> power of its apparent density (the inverse of porosity).<sup>(38)</sup> A relatively thinner more porous cortex offers less resistance to crack initiation and propagation should a fall occur.<sup>(9)</sup> Increasing the porosity of a relatively ‘compact’ structure like cortical bone reduces its strength more than increasing the porosity of an already porous structure like trabecular bone.<sup>(38)</sup> The reduction in stiffness of trabecular bone worsens to the third power of its apparent density. We suggest the higher porosity and relatively thinner cortices partly explain the higher incidence of fractures in taller women.

While our data confirm the work of Jepsen et al,<sup>(11)</sup> to the best of our knowledge, the association between height, relatively thinner and more porous cortices and higher risk for fracture has not been reported previously. Bell *et al.* have reported women with femoral neck fracture had thinner cortices, higher intracortical porosity assessed using histomorphometry and that these findings were associated with high intracortical remodelling.<sup>(39)</sup>

The study has several limitations. The association between porosity at the distal radius and fracture risk did not reach statistical significance, perhaps because of lack of power. Remodelling markers are more strongly associated with bone microarchitecture of the distal tibia than radius so a larger number of participants may be needed to detect a real association at this site.<sup>(18)</sup> The measurement method do

not allow us to determine the relative contributions of higher numbers of Haversian canals producing during growth from enlargement of existing Haversian canals during aging. Finally, variance in the degree of mineralization levels may contribute to differences in porosity but this is unlikely because in this group of middle-aged women, the variance in mineralization level was small (1 SD = 0.2%) compared with the variance in cortical porosity (1 SD ranged from 5.4 to 7.3 %). In the absence of diseases, there is little difference in the degree of mineralization between healthy individuals.<sup>(40)</sup>

Porosity was measured only at the distal tibia, fibula and radius. It is not known whether cortical porosity measured at the same bone that subsequently fractures will better predict that fracture. On average, taller women have wider bones but there is a great deal of variability. Another limitation is that many of the fractures occurred during childhood. We cannot exclude the possibility that trauma or high levels of physical activity during childhood could have contributed. Peripheral fractures are usually associated with a fall and it is not possible to quantify 'minimal' trauma and so further studies will be needed to the relative contributions of porosity and trauma to fractures. However, if this or other lifestyle factors contributed, this would weaken a true association between cortical porosity, relative cortical thickness and fractures. In addition, bone traits track during childhood and adulthood,<sup>(41,42)</sup> so we cannot distinguish whether women with higher cortical porosity and relatively thinner cortices attained this during growth or during aging or both.

In summary, as a long bone increases in length, it becomes wider and has a relatively larger medullary canal producing a relatively thinner cortex. Concomitant intracortical remodelling forms the intracortical Haversian-Volkmann canal network that appears as porosity in cross section. The excavation of the central medullary canal void volume distributes the mineralized bone volume radially in space achieving bending strength without compromising compressive strength. The mass needed to achieve this is minimized by greater radial distribution. Thus, taller women assemble wider

and relatively thinner cortices with higher porosity achieving the bone strength required for load bearing and lightness for mobility during young adulthood. These structural advantages become liabilities with longevity as intracortical and endocortical remodelling erodes a skeleton already assembled with relatively thinner and more porous cortices increasing fracture risk. Cortical porosity is likely to assist in identifying women with high risk for fracture and should be measured as part of risk assessment for fracture prevention.

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**Figure Legends**

**Fig. 1.** Distal tibia total cross sectional area (CSA), Medullary CSA, Medullary CSA/Total CSA and Cortical CSA/Total CSA as a function of height (upper panels). Cortical Porosity as a function of Height, Total CSA, Medullary CSA/Total CSA, a measure of relatively cortical thickness and cortical CSA/Total CSA (lower panel)

**Fig. 2.** A larger within twin pair difference in cortical porosity of the distal tibia is associated with a larger within twin pair differences in height, total cross sectional area (CSA), medullary CSA, and medullar CSA/Total CSA (a relatively thinner cortex).

**Fig. 3.** Higher probability of fracture is associated with a higher cortical porosity and a larger ratio of medullary cross sectional area (CSA) to total CSA, a surrogate reflecting a relatively thinner cortex.

**Table 1.** Trait mean  $\pm$  SD and associations between a 1 SD increment in height and a 1 SD increment in total cross-sectional area (CSA) and bone microarchitecture of the distal tibia, distal fibula and distal radius.

	Mean $\pm$ SD	1 SD greater height Estimate (95% CI)	1 SD larger TCSA Estimate (95% CI)
<b>Distal Tibia</b>			
Total bone CSA (mm <sup>2</sup> )	602 $\pm$ 98.5	0.69 (0.61, 0.77)	-
Medullary CSA (mm <sup>2</sup> )	386 $\pm$ 82.6	0.66 (0.58, 0.74)	1.00 (0.98, 1.03)
Cortical CSA (mm <sup>2</sup> )	216 $\pm$ 25.3	0.45 (0.34, 0.55)	0.64 (0.56, 0.72)
Medullary CSA/TCSA	0.64 $\pm$ 0.04	0.50 (0.41, 0.60)	0.79 (0.71, 0.87)
Cortical CSA/TCSA	0.36 $\pm$ 0.04	-0.50 (-0.60, -0.41)	-0.79 (-0.87, -0.71)
Cortical Porosity (%)	57.4 $\pm$ 5.4	0.42 (0.33, 0.52)	0.65 (0.56, 0.73)
Total vBMD (mg HA/cm <sup>3</sup> )	426 $\pm$ 69.9	-0.39 (-0.48, -0.30)	-0.61 (-0.70, -0.53)
Cortical vBMD (mg HA/cm <sup>3</sup> )	858 $\pm$ 86.9	-0.43 (-0.52, -0.33)	-0.65 (-0.74, -0.57)
Trabecular vBMD (mg HA/cm <sup>3</sup> )	175 $\pm$ 47.0	0.03 (-0.07, 0.14) <sup>a</sup>	0.01 (-0.09, 0.11) <sup>b</sup>
<b>Distal Fibula</b>			
Total bone CSA (mm <sup>2</sup> )	97.4 $\pm$ 21.7	0.47 (0.36, 0.58)	-
Medullary CSA (mm <sup>2</sup> )	35.7 $\pm$ 14.2	0.45 (0.35, 0.55)	0.94 (0.89, 1.00)
Cortical CSA (mm <sup>2</sup> )	61.7 $\pm$ 10.0	0.39 (0.28, 0.50)	0.83 (0.75, 0.91)
Medullary CSA/TCSA	0.35 $\pm$ 0.08	0.36 (0.25, 0.46)	0.72 (0.62, 0.82)
Cortical CSA/TCSA	0.65 $\pm$ 0.08	-0.36 (-0.46, -0.25)	-0.72 (-0.82, -0.62)
Cortical Porosity (%)	38.0 $\pm$ 7.3	0.29 (0.18, 0.39)	0.50 (0.40, 0.60)
Total vBMD (mg HA/cm <sup>3</sup> )	834 $\pm$ 153	-0.33 (-0.44, -0.23)	-0.62 (-0.72, -0.52)
Cortical vBMD (mg HA/cm <sup>3</sup> )	1170 $\pm$ 113	-0.29 (-0.40, -0.19)	-0.50 (-0.60, -0.41)
Trabecular vBMD (mg HA/cm <sup>3</sup> )	210 $\pm$ 96.1	-0.11 (-0.22, 0.00) <sup>c</sup>	-0.18 (-0.29, -0.07) <sup>d</sup>
<b>Distal Radius</b>			
Total bone CSA (mm <sup>2</sup> )	203 $\pm$ 34.2	0.58 (0.47, 0.69)	-
Medullary CSA (mm <sup>2</sup> )	122 $\pm$ 28.3	0.57 (0.46, 0.67)	1.00 (0.98, 1.03)
Cortical CSA (mm <sup>2</sup> )	81.7 $\pm$ 9.2	0.32 (0.20, 0.43)	0.65 (0.57, 0.73)
Medullary CSA/TCSA	0.59 $\pm$ 0.05	0.49 (0.39, 0.59)	0.78 (0.70, 0.87)
Cortical CSA/TCSA	0.41 $\pm$ 0.05	-0.49 (-0.59, -0.39)	-0.78 (-0.86, -0.70)
Cortical Porosity (%)	46.8 $\pm$ 6.2	0.30 (0.20, 0.41)	0.71 (0.62, 0.80)
Total vBMD (mg HA/cm <sup>3</sup> )	522 $\pm$ 95.9	-0.39 (-0.49, -0.29)	-0.71 (-0.80, -0.62)
Cortical vBMD (mg HA/cm <sup>3</sup> )	1032 $\pm$ 98.1	-0.31 (-0.41, -0.20)	-0.72 (-0.80, -0.63)
Trabecular vBMD (mg HA/cm <sup>3</sup> )	163 $\pm$ 58.0	-0.11 (-0.21, 0.00) <sup>e</sup>	-0.22 (-0.33, -0.11) <sup>f</sup>

Estimates are standardized coefficients in GEE models adjusted for age and weight, all  $p < 0.001$ , except for associations with trabecular volumetric bone mineral density (vBMD, mg/cm<sup>3</sup>), <sup>a</sup>  $p = 0.54$ , <sup>b</sup>  $p = 0.044$ , <sup>c</sup>  $p = 0.046$ , <sup>d</sup>  $p = 0.91$ , <sup>e</sup>  $p = 0.001$ , <sup>f</sup>  $p < 0.001$ .

**Table 2:** Mean, SD and comparison between fracture and non-fracture groups.

	Fracture		Non-fracture		p Value
	Mean	SD	Mean	SD	
Age	50.2	5.4	48.7	5.2	0.046
Height	163.4	6.3	162.3	5.5	0.124
Weight	70.8	14.0	69.2	14.9	0.902
<b>Distal Tibia</b>					
Total bone CSA (mm <sup>2</sup> )	613.9	116.0	597.3	90.9	0.086
Medullary CSA (mm <sup>2</sup> )	396.4	98.4	381.4	75.6	0.047
Cortical CSA (mm <sup>2</sup> )	217.5	27.6	215.9	24.3	0.868
Medullary CSA/TCSA	0.64	0.05	0.64	0.04	0.111
Cortical CSA/TCSA	0.36	0.05	0.37	0.04	0.111
Cortical Porosity (%)	58.7	5.7	57.0	5.2	0.012
Total vBMD (mg HA/cm <sup>3</sup> )	413.2	72.4	430.4	68.5	0.011
Cortical vBMD (mg HA/cm <sup>3</sup> )	838.0	91.7	865.1	84.0	0.013
Trabecular vBMD (mg HA/cm <sup>3</sup> )	167.9	37.3	177.1	50.1	0.031
<b>Distal Fibula</b>					
Total bone CSA (mm <sup>2</sup> )	99.3	22.9	96.7	21.2	0.447
Medullary CSA (mm <sup>2</sup> )	37.2	14.7	35.1	14.0	0.299
Cortical CSA (mm <sup>2</sup> )	62.1	10.9	61.5	9.71	0.873
Medullary CSA/TCSA	0.36	0.08	0.35	0.08	0.327
Cortical CSA/TCSA	0.64	0.08	0.65	0.08	0.327
Cortical Porosity (%)	40.3	7.7	37.1	6.9	0.002
Total vBMD (mg HA/cm <sup>3</sup> )	797.4	155.2	847.4	150.4	0.014
Cortical vBMD (mg HA/cm <sup>3</sup> )	1135	120.1	1183	107.2	0.003
Trabecular vBMD (mg HA/cm <sup>3</sup> )	192.4	90.3	217.1	97.6	0.008
<b>Distal Radius</b>					
Total bone CSA (mm <sup>2</sup> )	208.0	36.6	201.6	33.2	0.073
Medullary CSA (mm <sup>2</sup> )	125.2	30.7	120.2	27.3	0.091
Cortical CSA (mm <sup>2</sup> )	82.8	8.9	81.3	9.2	0.145
Medullary CSA/TCSA	0.60	0.05	0.59	0.05	0.407
Cortical CSA/TCSA	0.41	0.05	0.41	0.05	0.407
Cortical Porosity (%)	47.7	6.61	46.4	6.06	0.106
Total vBMD (mg HA/cm <sup>3</sup> )	505.8	99.2	527.9	94.1	0.050
Cortical vBMD (mg HA/cm <sup>3</sup> )	1016	104.4	1037	95.3	0.102
Trabecular vBMD (mg HA/cm <sup>3</sup> )	151.1	55.26	168.0	58.5	0.011

P-values for differences between fracture and non-fracture groups using GEE method.

**Table 3.** Fracture risk by 1 SD increment in height and bone microarchitecture.

Univariate analyses (1 SD unit)	Odds ratio (95% CI)	n Value
Age (5.3 years)	1.33 (1.03-1.73)	0.032
Height (6.3 cm)	1.19 (0.95-1.49)	0.130
Height <sup>2</sup>	1.28 (1.05-1.57)	0.017
<b>Distal Tibia</b>		
Total bone CSA (98.5 mm)	1.11 (0.89-1.39)	0.360
Total bone CSA <sup>2</sup>	1.22 (1.03-1.43)	0.021
Medullary CSA/Total CSA (0.04)	1.19 (0.96-1.48)	0.118
(Medullary CSA/Total CSA) <sup>2</sup>	1.37 (1.17-1.61)	< 0.001
Cortical porosity (5.4%)	1.38 (1.09-1.77)	0.009
Cortical vBMD (86.9 mg HA/cm <sup>3</sup> )	0.73 (0.57-0.93)	0.010
Trabecular vBMD (47.0 mg HA/cm <sup>3</sup> )	0.82 (0.66-1.02)	0.074
<b>Distal Fibula</b>		
Total bone CSA (21.7 mm <sup>2</sup> )	1.15 (0.91-1.45)	0.238
Medullary CSA/Total CSA (0.08)	1.15 (0.90-1.47)	0.255
Cortical porosity (7.3%)	1.53 (1.21-1.95)	< 0.001
Cortical vBMD (113 mg HA/cm <sup>3</sup> )	0.65 (0.52-0.83)	< 0.001
Trabecular vBMD (96.1 mg HA/cm <sup>3</sup> )	0.77 (0.61-0.97)	0.024
<b>Distal Radius</b>		
Total bone CSA (34.2 mm <sup>2</sup> )	1.19 (0.93-1.51)	0.168
Medullary CSA/Total CSA (0.05)	1.08 (0.84-1.38)	0.557
Cortical porosity (6.2%)	1.22 (0.96-1.55)	0.108
Cortical vBMD (98.1 mg HA/cm <sup>3</sup> )	0.82 (0.64-1.04)	0.106
Trabecular vBMD (58.0 mg HA/cm <sup>3</sup> )	0.76 (0.60-0.97)	0.025
<b>Multivariable logistic regression analyses</b>		
<b>Distal Tibia</b>		
Height (6.3 cm)	1.11 (0.85-1.45)	0.440
Height <sup>2</sup>	1.21 (0.97-1.50)	0.085
Medullary CSA/TCSA (0.04)	0.86 (0.63-1.19)	0.372
Medullary CSA/TCSA) <sup>2</sup>	1.34 (1.13-1.58)	0.001
Cortical porosity (5.4%)	1.55 (1.11-2.15)	0.009
<b>Distal Fibula</b>		
Height (6.3 cm)	1.09 (0.86-1.39)	0.473
Height <sup>2</sup>	1.24 (1.00-1.52)	0.046
Cortical porosity (7.3%)	1.47 (1.14-1.88)	0.003
<b>Distal Radius</b>		
Height (6.3 cm)	1.18 (0.94-1.48)	0.155
Height <sup>2</sup>	1.27 (1.04-1.56)	0.019
Trabecular vBMD (58.0 mg HA/cm <sup>3</sup> )	0.77 (0.61-0.98)	0.037

Odds ratio per 1 SD unit in logistic regression analyses using quadratic GEE models adjusted for age, height and weight in the final models when p-value < 0.05.

CSA, cross sectional area. vBMD, volumetric bone mineral density.

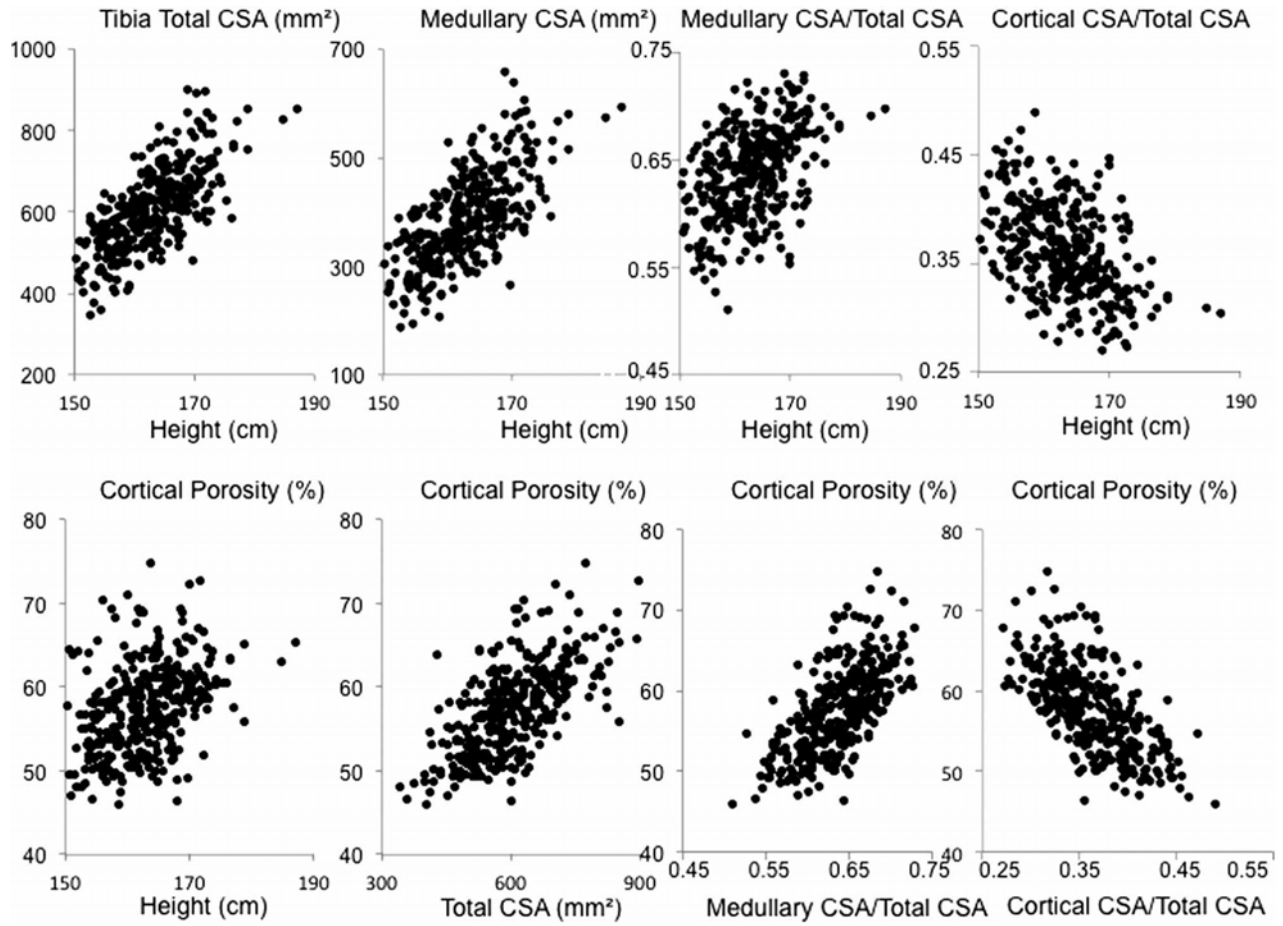


Figure 1

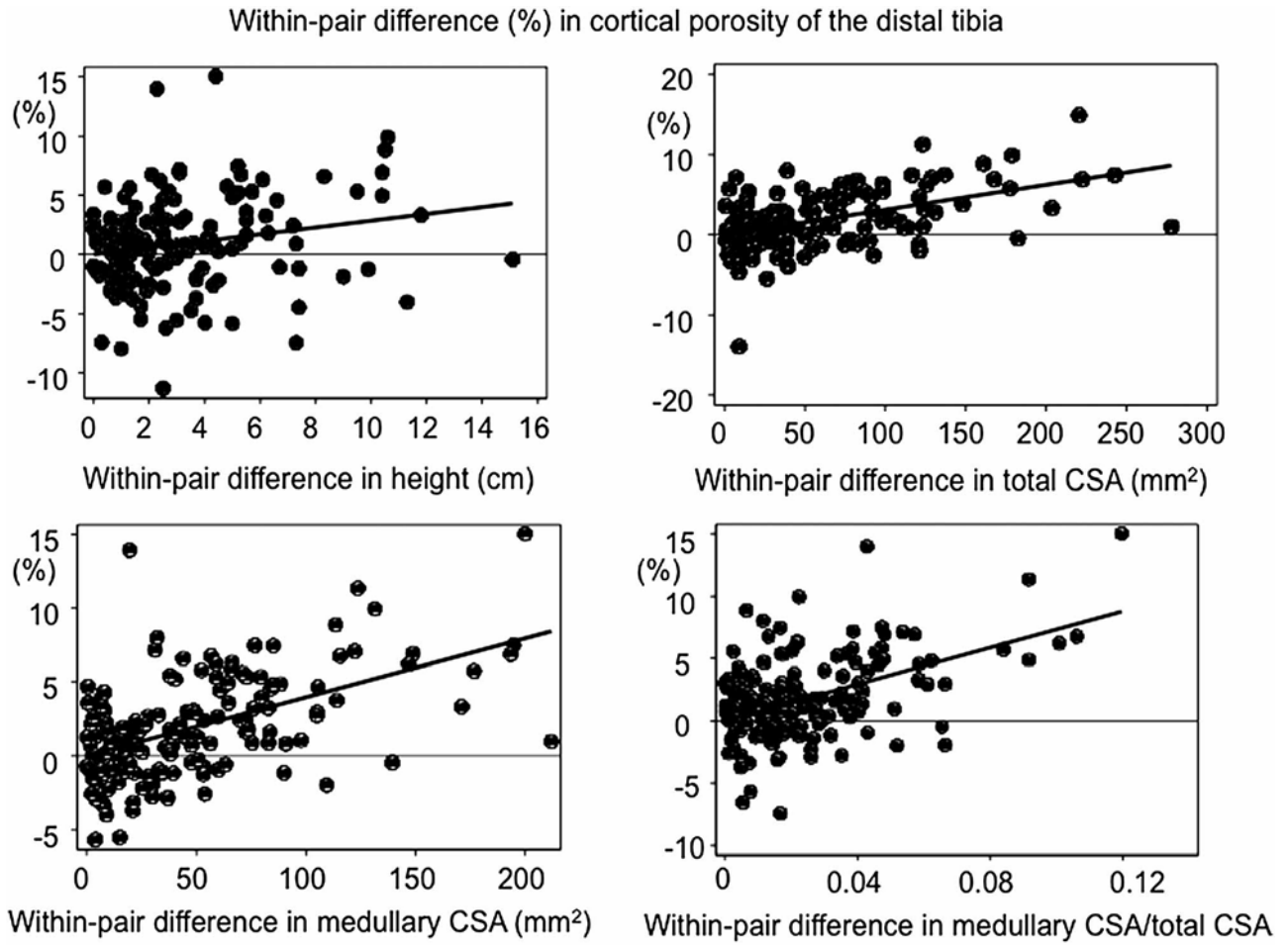


Figure 2

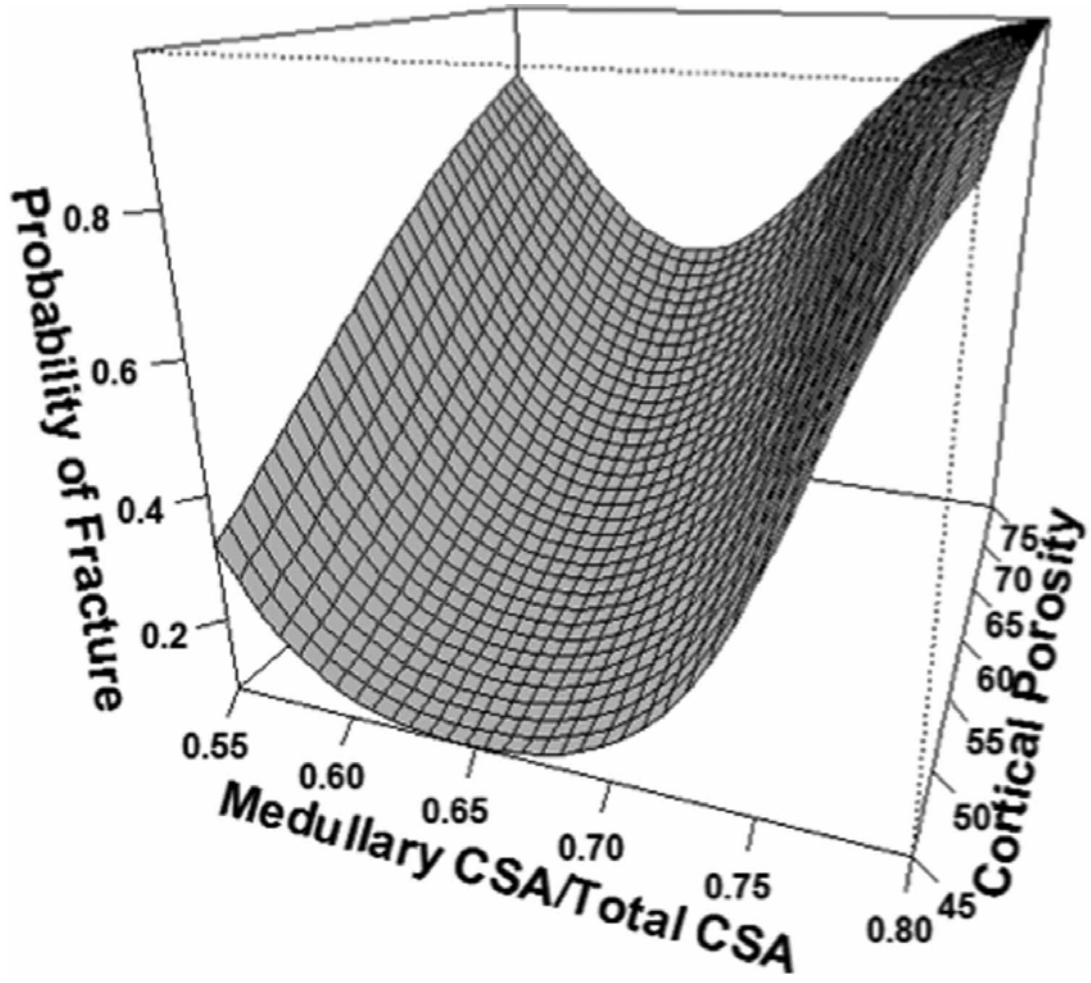


Figure 3





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