Cortical and trabecular bone microarchitecture as an independent predictor of incident fracture risk in older women and men in the Bone Microarchitecture International Consortium (BoMIC): a prospective study

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See **Comment** page 5

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Summary

Background Although areal bone mineral density (aBMD) assessed by dual-energy x-ray absorptiometry (DXA) is the clinical standard for determining fracture risk, most older adults who sustain a fracture have T scores greater than –2·5 and thus do not meet the clinical criteria for osteoporosis. Importantly, bone fragility is due to low BMD and deterioration in bone structure. We assessed whether indices of high-resolution peripheral quantitative CT (HR-pQCT) were associated with fracture risk independently of femoral neck aBMD and the Fracture Risk Assessment Tool (FRAX) score.

Methods We assessed participants in eight cohorts from the USA (Framingham, Mayo Clinic), France (QUALYOR, STRAMBO, OFELY), Switzerland (GERICO), Canada (CaMos), and Sweden (MrOS). We used Cox proportional hazard ratios (HRs) to estimate the association between HR-pQCT bone indices (per 1 SD of deficit) and incident fracture, adjusting for age, sex, height, weight, and cohort, and then additionally for femoral neck DXA aBMD or FRAX.

Findings 7254 individuals (66% women and 34% men) were assessed. Mean baseline age was 69 years (SD 9, range 40–96). Over a mean follow-up of 4·63 years (SD 2·41) years, 765 (11%) participants had incident fractures, of whom 633 (86%) had femoral neck T scores greater than –2·5. After adjustment for age, sex, cohort, height, and weight, peripheral skeleton failure load had the greatest association with risk of fracture: tibia HR 2·40 (95% CI 1·98–2·91) and radius 2·13 (1·77–2·56) per 1 SD decrease. HRs for other bone indices ranged from 1·12 (95% CI 1·03–1·23) per 1 SD increase in tibia cortical porosity to 1·58 (1·45–1·72) per 1 SD decrease in radius trabecular volumetric bone density. After further adjustment for femoral neck aBMD or FRAX score, the associations were reduced but remained significant for most bone parameters. A model including cortical volumetric bone density, trabecular number, and trabecular thickness at the distal radius and a model including these indices plus cortical area at the tibia were the best predictors of fracture.

Interpretation HR-pQCT indices and failure load improved prediction of fracture beyond femoral neck aBMD or FRAX scores alone. Our findings from a large international cohort of men and women support previous reports that deficits in trabecular and cortical bone density and structure independently contribute to fracture risk. These measurements and morphological assessment of the peripheral skeleton might improve identification of people at the highest risk of fracture.

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Introduction

Fragility fractures, which lead to substantial morbidity, mortality, and expense, are a public health concern. Notably, the number of women who have fractures per year exceeds the combined number with incident stroke, breast cancer, and myocardial infarction. Annual costs associated with fragility fractures exceed US$19 billion in the USA and €36 billion in Europe.[1] Given the predicted growth in the number of older adults, the number of fractures and associated costs are projected to increase by two to four times worldwide in the next few decades. Meanwhile, osteoporosis remains underdiagnosed and undertreated.[2]

Diagnosis of osteoporosis and prediction of fracture risk rely on case-finding strategies based on measurement of bone mineral density (BMD) by dual-energy x-ray

Research in context

Evidence before this study

We searched PubMed with the terms "HR-pQCT", "microarchitecture", "fracture", and "epidemiology". Previous work was largely limited to case-control studies of fracture history, cortical and trabecular bone density, and microarchitecture assessed by high-resolution peripheral quantitative CT (HR-pQCT) at peripheral skeletal sites. Bone measurements from HR-pQCT differentiated individuals with history of fracture from non-fracture controls, often independently of areal bone-mineral density (aBMD) measured by dual-energy x-ray absorptiometry (DXA). Since this study was planned, a few prospective studies have shown that HR-pQCT bone measurements predict incident fractures independently of DXA aBMD and, in some cases, the Fracture Risk Assessment Tool (FRAX), which estimates the 10-year probability of fracture. Those studies, however, were limited by few incident fractures and none included women and men together.

Added value of this study

The Bone Microarchitecture International Consortium includes data for 7254 older women and men from eight cohorts in North America and Europe. Our analysis showed that HR-pQCT measures of cortical and trabecular peripheral bone density and microstructure and estimated failure load predicted incident fractures independently of femoral neck aBMD and FRAX, with a doubling in risk of fracture per 1 SD decrease in failure load after adjustment for age, sex, height, weight, and femoral neck aBMD or FRAX. Cortical density, cortical area, trabecular number, and trabecular thickness formed the best set of fracture predictors. The findings applied to populations with BMD T scores greater than −2·5, indicating that older women and men without osteoporosis exhibited deficits in bone microarchitecture. Failure load calculated by microfinite element analysis was a powerful predictor of fracture risk and performed as well as or better than the best combination of individual HR-pQCT bone parameters.

Implications of all the available evidence

Our findings support previous reports that deficits in trabecular and cortical bone density and structure independently contribute to fracture risk. They also highlight the importance of compartment-specific assessments of bone density and microstructure when assessing skeletal fragility. As most of our study participants with fractures had femoral neck aBMD T scores in the osteopenic or normal range, our results indicate that assessment of bone microstructure might be useful in people who would not otherwise be identified as being at risk of fracture. Therefore, while femoral neck aBMD and FRAX remain the clinical standards for risk stratification, assessment of additional bone traits might improve prediction of fracture risk.

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absorptiometry (DXA), combined with assessment of clinical risk factors with the Fracture Risk Assessment Tool (FRAX), which predicts 10-year fracture risk. However, most fractures occur in individuals who have not been diagnosed as having osteoporosis by BMD testing, have few clinical risk factors, or both. In these people FRAX score would indicate a low probability of fracture.[3] Improved methods to identify people at the highest risk of fracture would allow for treatment of patients who would probably have the greatest benefit-to-risk profiles, and might ultimately reduce fracture burden.

Whole-bone strength is determined by bone mass, morphology, and microarchitecture. As DXA-based BMD assesses only bone mass, other techniques are needed to assess bone morphology and microstructure. Trabecular bone score, a two-dimensional textural measurement derived from a posteroanterior lumbar spine DXA scan, slightly improves prediction of the risk of hip fracture compared with BMD alone, but does not improve assessment of vertebral or major osteoporotic fracture.[4] CT can be used to assess cortical and trabecular bone at central skeletal sites, but lacks the resolution to provide information about bone microstructure. High-resolution peripheral quantitative CT (HR-pQCT) shows cortical and trabecular bone density and microarchitecture at peripheral skeletal sites with minimum radiation exposure and can differentiate between individuals with and without a history of fracture, often independently of DXA BMD.[5–10] A few studies have also shown that HR-pQCT can predict incident fractures in men[11–13] and women[14,15] independently of DXA BMD and, in some cases, FRAX. These studies, however, have been limited by low numbers of incident fractures (n=71–135) and none included women and men together.

We did a prospective multinational cohort study to investigate whether peripheral bone density and microstructure predict incident fracture in older women and men, and whether they do so independently of femoral neck DXA BMD and FRAX. We selected DXA BMD of the femoral neck, because this site is most widely used for fracture prediction and is included in FRAX. We also aimed to determine the combination of HR-pQCT variables that were most strongly associated with incident fracture. Based on previous studies,[11,14–16] our primary hypothesis was that lower trabecular bone density, cortical area, and failure load (calculated from microfinite element analyses [μFEA]) at the radius and tibia would be predictors of incident fracture risk independently of DXA BMD and FRAX.

Methods

Study design and participants

This was a prospective study by the Bone Microarchitecture International Consortium (BoMIC), which includes participants who are members of eight cohorts: the Framingham Study[17] and the Mayo Clinic[18] in the

USA; Qualité Osseuse Lyon Orléans (QUALYOR),[19] Structure of Aging Men's Bones (STRAMBO),[20] and Os des Femmes de Lyon (OFELY)[21] in France; Geneva Retirees Cohort (GERICO)[22] in Switzerland; Canadian Multicentre Osteoporosis Study (CaMos)[23] in Canada; and Osteoporotic Fractures in Men Study (MrOS)[24] in Sweden (table 1). These cohorts were established to study risk factors for osteoporosis by comprehensive clinical examinations, standardised questionnaires, and ascertainment of incident fractures through self-report by participants, medical records, confirmation by medical professionals or trained research staff, or a combination of these methods. We assessed data from individuals who had undergone HR-pQCT scanning and were aged at least 40 years. Follow-up time was defined as the number of years contributed by a participant from HR-pQCT scanning to the first fracture, death, last contact, or the cohort's study closing date. Participants in each cohort had provided written informed consent to enter the relevant studies, and the Institutional Review Board for Human Research at Hebrew SeniorLife approved this study.

HR-pQCT

Volumetric bone density (vBMD) and bone microarchitecture were assessed at the ultradistal tibia and ultradistal radius with XtremeCT scanners (Scanco Medical, Switzerland), which were used at all study sites by operators trained by the manufacturer and who followed the same protocol for scan acquisition and analysis. Scans were acquired with a nominal isotropic voxel size of 82 µm³. Scanning was done on the non-dominant forearm and the leg on the same side, except in the Framingham Study cohort, in which right legs were always scanned, and in the CaMos and MrOS cohorts, in which left legs were always scanned. If a participant reported previous extremity fracture or had metal in the scan region, the contralateral extremity was examined. Anteroposterior scout views were used to place a reference line on the distal tibial and radial joint surfaces.[25] The scan region was 9 mm in length (110 slices) and offset proximally to the reference line by 22·5 mm for the tibia and 9·5 mm for the radius. Scanning of a quality control phantom limb containing rods of hydroxyapatite at densities of 0, 100, 200, 400, and 800 mg hydroxyapatite per cm³ was done daily to monitor long-term stability of the system.

At each clinical site, scans were graded with a five-point motion artifact scale (1=none, 2=minor, 3=moderate, 4=severe, and 5=extreme).[26] For density measures, scans with movement artifacts graded 1–4 were retained and for microarchitectural measures those graded 1–3 were

	All participants (n=7254)	Framingham,[17] USA (n=1582)	Mayo Clinic,[18] USA (n=364)	QUALYOR,[19] France (n=1504)	STRAMBO,[20] France (n=810)	OFELY,[21] France (n=753)	GERICO,[22] Switzerland (n=912)	CaMos,[23] Canada (n=838)	MrOS,[24] Sweden (n=491)
Women/men	4768 (66%)/ 2486 (34%)	898 (57%)/ 684 (43%)	200 (55%)/ 164 (45%)	1504 (100%)/ 0	0/ 810 (100%)	753 (100%)/ 0	727 (80%)/ 185 (20%)	686 (82%)/ 152 (18%)	0/ 491 (100%)
Age (years)	69 (9)	71 (8)	64 (13)	66 (7)	72 (7)	63 (12)	65 (1)	72 (9)	80 (4)
BMI (kg/m²)	27 (5)	28 (5)	29 (6)	25 (4)	28 (4)	25 (4)	25 (4)	28 (5)	26 (3)
Osteoporosis medication use*	789 (11%)	135 (9%)	56 (16%)	N/A†	31 (4%)	165 (22%)	179 (20%)	215 (26%)	8 (2%)
Previous fracture	1664 (23%)	444 (28%)	229 (63%)	N/A†	168 (21%)	125 (17%)	331 (36%)	307 (37%)	60 (12%)
Femoral neck aBMD (g/cm²)	0·79 (0·13)	0·83 (0·13)	0·84 (0·15)	0·73 (0·07)	0·87 (0·14)	0·80 (0·12)	0·80 (0·12)	0·74 (0·14)	0·78 (0·13)
FRAX for hip fracture (%)‡	2 (4)	2 (3)	3 (5)	2 (2)	2 (2)	2 (4)	2 (2)	3 (5)	5 (5)
FRAX for major osteoporotic fracture (%)‡	9 (6)	10 (6)	11 (9)	6 (4)	4 (3)	7 (6)	11 (6)	13 (8)	10 (6)
T score									
≤–2·5	537 (8%)	62 (4%)	22 (6%)	115 (8%)	27 (3%)	49 (7%)	62 (7%)	185 (23%)	15 (3%)
>–2·5 to <–1·0	3843 (54%)	754 (49%)	142 (39%)	1232 (82%)	287 (36%)	392 (52%)	479 (53%)	388 (49%)	169 (34%)
≥–1·0	2714 (38%)	726 (46%)	192 (54%)	157 (10%)	489 (60%)	307 (41%)	366 (40%)	226 (27%)	251 (58%)
Duration of follow-up (years)	4·6 (2·4)	3·5 (1·1)	2·9 (1·1)	3·7 (0·8)	7·3 (2·5)	8·1 (2·6)	5·1 (1·9)	3·0 (1·2)	3·8 (2·2)
Incident fracture	765 (11%)§¶	47 (3%)	34 (9%)	153 (10%)	90 (11%)	164 (22%)	118 (13%)	80 (10%)	79 (16%)
Death	403 (6%)	68 (4%)	11 (3%)	7 (<1%)	156 (19%)	32 (4%)	0	25 (3%)	104 (21%)
Lost to follow-up	573 (8%)	0	0	75 (5%)	66 (8%)	46 (6%)	0	67 (8%)	0

Data are n (%) or mean (SD). Numbers of participants might not add up to totals at the top of the columns because of missing data. aBMD=areal bone mineral density. FRAX=Fracture Risk Assessment Tool. N/A=not applicable. *Does not include calcium or vitamin D supplements. †Exclusion criterion for the QUALYOR cohort. ‡Calculated with BMD. §In total consortium 150 (20%) wrist, 122 (16%) spine, 92 (12%) rib, 72 (9%) ankle, 68 (9%) hip, 63 (8%) upper arm, and 198 (26%) other. ¶509 (67%) due to fall from standing height or lower, 145 (19%) due to fall from greater than standing height or trauma, 111 (15%) information not available.

Table 1: **Characteristics of participants in the Bone Microarchitecture International Consortium**

retained. A standard analysis programme (Scanco software version 6.0) was used to assess total cross-sectional area, density, trabecular density, and trabecular microarchitecture, and a semi-automated cortical bone segmentation technique was used to assess cortical density and cortical microarchitecture.[27] The central coordinating site reviewed the data from each cohort for outliers and consistency.

µFEA

Failure load was estimated by linear µFEA with Scanco Image Processing Language version V5.16/FE-v01.16 for OFELY, GERICO, and MrOS and with FAIM version 8.0 for CaMos, Framingham, and Mayo Clinic.[28] No µFEA was done in the QUALYOR (n=1504 women) or STRAMBO (n=810 men) cohorts. Briefly, axial compression conditions were applied with 1% apparent strain. Failure load was defined as the load when 2% of the elements exceeded a strain of 0·007. Boundary conditions used in cohorts were either axial or uniaxial loading, and a range of tissue moduli were used (6·829–20 GPa). To harmonise failure load across cohorts, we linearly calibrated to approximate axial conditions with a tissue modulus of 6·829 GPa. The calibration curves were generated by solving a large subgroup (n=1371) with variations of boundary conditions and tissue moduli.[29] The root mean square estimated error for calibration was between 1·82 and 3·99%. 277 tibia scans and 649 radius scans were excluded due to motion artifacts.

DXA BMD

Areal BMD (aBMD) at the femoral neck and ultradistal radius was assessed with Hologic DXA scanners (Marlborough, MA, USA) in QUALYOR, GERICO, STRAMBO, OFELY, and MrOS, with Lunar DXA scanners (GE Healthcare, Madison, WI, USA) in the Framingham and Mayo Clinic cohorts, and with both systems in the CaMos cohort (dependent on the study site). We standardised femoral neck aBMD values and calculated T scores with published equations.[30]

FRAX assessment

Each cohort provided FRAX scores for major osteoporotic fracture and hip fracture calculated with femoral neck aBMD.[31] We used only FRAX for major osteoporotic fracture in our analyses. FRAX calculates 10-year fracture probability specific to country and race that is based on 12 clinical risk factors (age, sex, weight, height, previous fracture, parent fractured hip, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol consumption, and femoral neck DXA aBMD). A minimum of age, sex, weight, and height are required to calculate FRAX. If information is unavailable for any other input, the algorithm assumes a response of "no" for those items.[31] The studies did not provide the distributions of missing data for variables used in the FRAX calculation for the cohorts.

Covariates

Each cohort provided information on covariates obtained at the time of the HR-pQCT scanning. Weight and height were measured with standard methods. BMI was calculated as weight divided by height squared. Information on age, smoking, alcohol consumption, and use of osteoporosis medication was obtained with questionnaires. History of fracture during adulthood was ascertained with a combination of data collected via questionnaires and active surveillance in each cohort. We defined previous fractures as non-traumatic and traumatic fracture throughout adulthood, excluding those of the skull, finger, toe, hand, foot, and ankle and pathological fractures.

Outcomes

Our primary outcome was incident fracture, defined as the first non-traumatic or traumatic fracture after HR-pQCT other than fractures to the skull, face, sternum, fingers, and toes and pathological fractures. We also excluded non-clinical spine fractures because few cohorts did serial radiological assessments. As a secondary outcome we assessed major osteoporotic fracture, defined as incident fractures of the proximal humerus, wrist, distal forearm, clinical spine, or hip.[25]

Statistical analysis

We used Cox proportional hazard regression models to calculate hazard ratios (HRs) and 95% CIs for the association between individual bone traits and incidence of fracture. We did the analysis with individual-level data for all cohorts except MrOS, where individual-level data were not available. We analysed MrOS separately and did meta-analyses based on cohort-level data.

We standardised each bone parameter to SD units and expressed outcomes as HRs per 1 SD deficit. We defined a set of base covariates (age, sex, cohort, height, and weight). To evaluate whether HR-pQCT indices independently predicted fracture risk, we compared a model adjusted for the base covariates with one that included the base covariates plus femoral neck aBMD and a model adjusted only for cohort with one adjusted for cohort and FRAX (for major osteoporotic fracture).

To identify the set of HR-pQCT bone indices that best predicted incident fracture (in all cohorts except MrOS), we first identified the bone indices nominally associated with incident fracture in a bivariate analysis. Second, we did a correlation analysis involving all bone measures and selected variables that were not strongly correlated with each other (r<0·80). Third, we used a variance inflation factor to further assess potential multicollinearity and excluded bone measures with variance inflation factors greater than 30. Finally, we used a best subsets selection procedure (global score statistic) and Akaike information criterion to select the bone measures for the final model. We used Harrell's concordance statistic to quantify the predictive ability of models.[32]

With a bootstrap method using 2000 samples, we estimated SEs and constructed CIs to test differences in the predictive ability of models. Fourth, we compared the predictive accuracy of models that included the best set of HR-pQCT indices plus femoral neck aBMD with that of models that included femoral neck aBMD alone or FRAX alone. Finally, we compared the predictive accuracy of models including μFEA failure load with models that included femoral neck aBMD alone.

We did four secondary analyses. First, we repeated the primary analysis in women and men separately to provide sex-specific results for individual bone traits and incident fracture. Second, we explored whether associations between radius HR-pQCT indices and incident fracture persisted after adjustment for DXA aBMD in the same ultradistal radius site. DXA aBMD of the radius was not done at the time of HR-pQCT scanning in CaMos (n=838) and MrOS (n=491), and data on this measurement were missing from 182 individuals in other cohorts. Therefore, we consider this analysis to be exploratory. Third, we compared the predictive accuracy of models that included the best set of HR-pQCT parameters plus radius aBMD with models that included radius aBMD alone, and compared those including μFEA failure load plus radius aBMD with models including radius aBMD alone. Fourth, we did a net reclassification improvement analysis to compare models that included the best set of HR-pQCT measures plus femoral neck aBMD with models that included femoral neck aBMD alone, and compared those with μFEA failure load plus femoral neck aBMD with models that included femoral neck aBMD alone. We used Cox proportional hazards models to generate predicted probabilities of fractures at 5 years and to estimate continuous (category-free) net reclassification improvement.

Significance was indicated by p values less than 0·05 unless otherwise indicated. All statistical analyses were done with SAS version 9.4.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We assessed data from 7254 participants (4768 women and 2486 men) with a mean age of 69 years (SD 9, range 40–96; table 1). The mean duration of follow-up for incident fractures was 4·63 years (SD 2·41, range 0·01–11·04 years). 11% of participants were taking osteoporosis medications and 23% had had previous fractures. The mean FRAX score was 2% (SD 4%) for hip fracture and 9% (SD 6%) for major osteoporosis fracture. More than half of participants had femoral neck T scores in the osteopenia range, and only 8% had values in the osteoporosis category (<–2·5).

Incidence rate was 22·54 fractures per 10^3 person-years. Cumulative overall incidence was 11% (765 fractures in 7254 participants). 551 (12%) of 4768 women and 214 (9%) of 2486 men had incident fractures (table 2). The distribution of fracture sites was 150 (20%) in the wrist, 122 (16%) in the spine, 92 (12%) in the ribs, 72 (9%) in the ankle, 68 (9%) in the hip, 63 (8%) in the proximal humerus, and 198 (26%) at other sites. Most incident fractures (509 [67%]) were due to falls from standing height or lower and 145 (19%) were attributed to falls from greater than standing height or to trauma. The degree of trauma was unknown for the remaining 111 (15%) fractures. The cumulative incidence of major

	Incident fracture (n=7254)		Incident fracture in women (n=4768)		Incident fracture in men (n=2486)	
	Yes (n=765)	No (n=6489)	Yes (n=551)	No (n=4217)	Yes (n=214)	No (n=2272)
Age (years)	70 (10)*	69 (9)	68 (9)*	67 (9)	75 (8)*	72 (9)
BMI (kg/m²)	26 (5)*	27 (5)	26 (5)	26 (5)	27 (4)*	28 (4)
Osteoporosis medication use	121 (16%)*	668 (10%)	109 (20%)*	620 (15%)	12 (6%)*	48 (2%)
Previous fragility fracture	234 (31%)*	1430 (22%)	164 (30%)*	820 (19%)	70 (33%)*	610 (27%)
Femoral neck aBMD (g/cm²)	0·75 (0·12)†	0·80 (0·13)	0·74 (0·11)*	0·77 (0·11)	0·78 (0·14)*	0·85 (0·14)
T score						
≤–2·5	103 (14%)*	434 (7%)	93 (17%)*	370 (9%)	10 (5%)	64 (3%)
>–2·5 to <–1·0	443 (60%)*	3400 (53%)	347 (64%)*	2642 (64%)	96 (51%)*	758 (34%)
≥–1·0	190 (26%)*	2524 (40%)	106 (19%)*	1145 (28%)	84 (44%)*	1379 (63%)
FRAX score for hip fracture (%)	4 (5)*	2 (4)	4 (5)*	2 (4)	4 (6)*	2 (3)
FRAX score for major osteoporotic fracture (%)	11 (8)*	9 (6)	12 (9)*	10 (7)	9 (7)*	7 (4)

Data are n (%) or mean (SD). Numbers of participants might not add up to totals at the top of the columns because of missing data. aBMD=areal bone mineral density. FRAX=Fracture Risk Assessment Tool. *p<0·05 for difference from those without incident fractures.

Table 2: **Characteristics of participants by incident fracture status**

osteoporotic fracture was 6% (n=403) or 11·88 fractures per 10^3 person-years.

Factors associated with incident fracture were older age, female sex, slightly lower BMI, use of osteoporosis medication, previous fracture, lower T score, and higher FRAX score (table 2). Unadjusted analyses showed that nearly all HR-pQCT bone measures were worse in individuals who sustained an incident fracture than in those who did not (appendix). In women, most incident fractures occurred in those with baseline femoral neck T scores in the osteopenic range (table 2).

In the base model adjusted for age, sex, cohort, height, and weight, the association between femoral neck aBMD and incident fracture was increased (HR 1·57, 95% CI 1·42–1·74, per 1 SD decrease; figure). The strongest association with fracture was seen for µFEA failure load at the distal tibia (HR 2·40, 95% CI 1·98–2·91) and distal radius (2·13, 1·77–2·56). Risk of fracture was increased by around 10–60% per 1 SD deficit for most other bone indices at the tibia and radius (range from HR 1·12, 95% CI 1·03–1·23, for tibia cortical porosity to 1·58, 1·45–1·72, for radius trabecular vBMD; figure, appendix). Total area was not associated with incident fracture (tibia HR 0·88, 0·77–1·00, and radius 1·01, 0·87–1·16). The HR for the association between FRAX and incident fracture was 1·40 (1·32–1·48).

After adjustment for the base covariates plus femoral neck aBMD, associations between HR-pQCT parameters and incident fractures were attenuated but remained significant for most parameters (figure). Failure load retained the strongest association with fracture in the distal tibia (HR 1·98, 95% CI 1·58–2·49) and distal radius (1·82, 1·47–2·25). Other significant HRs ranged from 1·09 (95% CI 1·04–1·14) for tibia SD trabecular number to 1·44 (1·31–1·59) for radius trabecular vBMD (appendix). By contrast, tibia cortical thickness and trabecular thickness and radius cortical vBMD and cortical tissue mineral density were no longer associated with fracture after adjustment for femoral neck aBMD (figure).

After adjusting for cohort and FRAX, associations with incident fracture remained significant for all HR-pQCT parameters at the tibia and radius except for cortical porosity and total area, which remained weakly or not associated with fracture risk (figure). Failure load continued to have the strongest association at the tibia and radius (HR 1·78, 95% CI 1·50–2·12 for tibia, 1·76, 1·48–2·09 for radius), followed by trabecular vBMD (radius 1·51, 1·38–1·65; tibia 1·32, 1·21–1·44), total vBMD (radius 1·43, 1·31–1·56; tibia 1·41, 1·29–1·54), trabecular number (radius, 1·39, 1·27–1·51; tibia 1·19, 1·09–1·30), and cortical area (radius 1·37, 1·23–1·52; tibia, 1·38, 1·25–1·53).

When the outcome was restricted to incident major osteoporotic fracture, the HRs were generally similar to or stronger than those for all fractures (appendix). After additional adjustment for femoral neck aBMD,

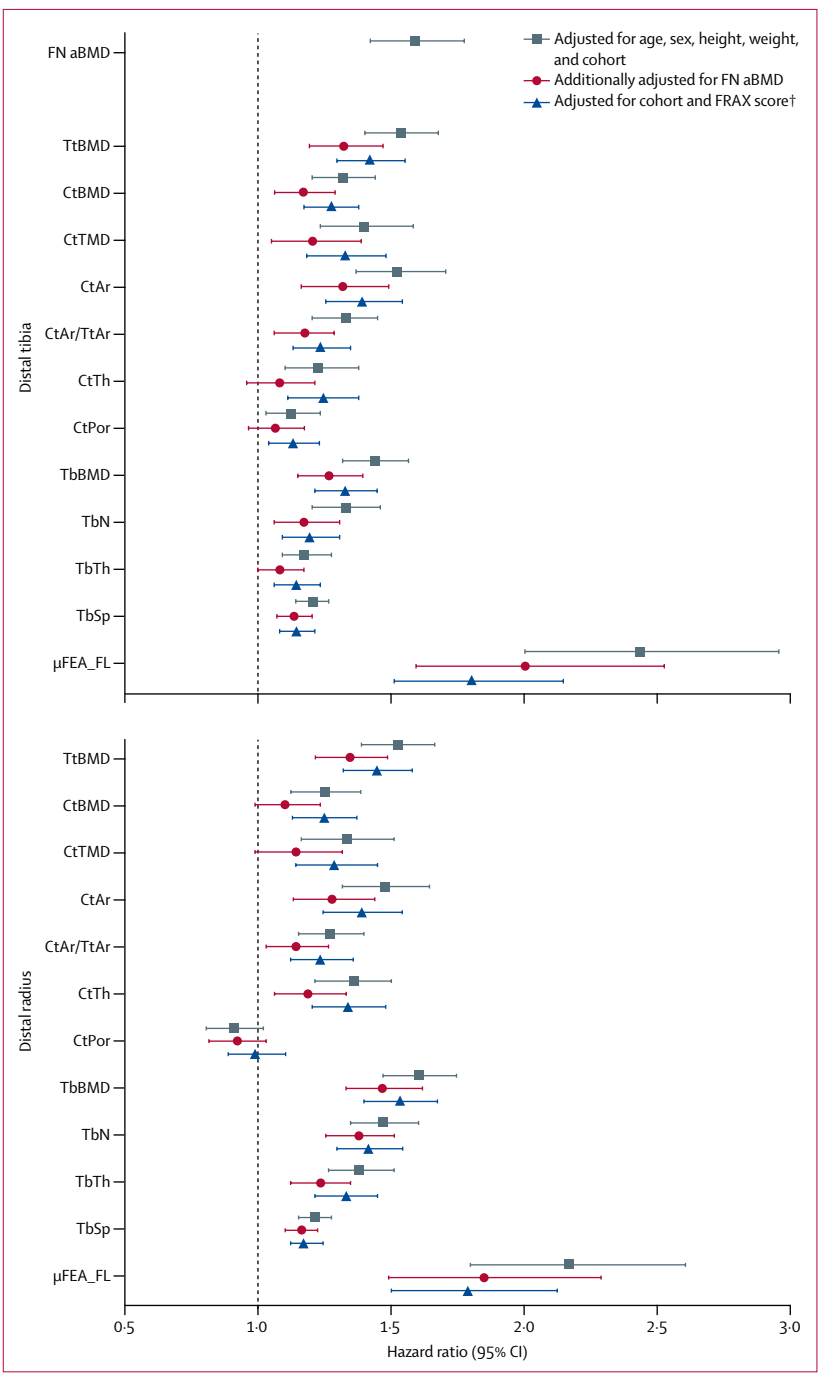

Figure: **Associations between FN aBMD and HR-pQCT indices at the tibia and radius for any incident fracture***
Data are hazard ratios and 95% CIs per 1 SD change in the bone measure in the expected direction of increased fracture risk. Numerical data are available in the appendix. FN aBMD=femoral neck areal bone mineral density assessed by dual x-ray absorptiometry. TtBMD=total (integral) volumetric bone mineral density. CtBMD=cortical volumetric bone mineral density. CtTMD=cortical tissue mineral density. CtAr=cortical area. CtAr/TtAr=cortical area proportion. CtTh=cortical thickness. CtPor=cortical porosity. TbBMD=trabecular volumetric bone mineral density. TbN=trabecular number. TbTh=trabecular thickness. TbSp=trabecular separation. µFEA_FL=microfinite element analysis failure load. *Includes all sites except skull, face, sternum, finger, and toe and excludes pathological fractures. †FRAX score is for major osteoporotic fracture.

associations with major osteoporotic fracture were attenuated but remained significant for most of the same bone parameters as for associations with all fractures.

See Online for appendix

In sex-stratified analyses, we found that results for incident fracture were largely similar in women and men, although effect sizes were somewhat attenuated in men (appendix). In secondary analyses in which we adjusted for radial DXA aBMD (rather than femoral neck aBMD), we found independent associations for fracture with radius trabecular number (1·18, 95% CI 1·04–1·33) and radius trabecular vBMD (1·26, 1·09–1·46; appendix). No other HR-pQCT measures in the radius showed significant associations after adjustment for radius DXA aBMD, and CIs were in the range 0·9–1·2 (appendix).

We identified cortical density, trabecular number, and trabecular thickness at the distal radius and these variables plus cortical area at the tibia as the best sets of non-collinear predictors for fracture. Furthermore, these sets of predictors improved the ability to predict fracture beyond femoral neck aBMD and FRAX (table 3). Addition of μFEA failure load improved the area under the curve for the distal radius and tibia compared with femoral neck aBMD alone (table 4). Repeating this analysis for major osteoporotic fracture yielded larger areas under the curve than those estimated for all incident fractures (appendix). The best set of predictors significantly improved the ability to predict major osteoporotic fracture beyond femoral neck aBMD, at the radius but not at the tibia (appendix). Models for major osteoporotic fracture with μFEA failure load at the radius and tibia did not improve the area under the curve compared with femoral neck aBMD alone (appendix).

Compared with the areas under the curve for DXA aBMD at the ultradistal radius, fracture prediction did not significantly improve when the best set of radius HR-pQCT parameters or radius failure load were added to the model (appendix). In analyses of net reclassification improvement, when HR-pQCT indices were compared with femoral neck aBMD alone, 11% of fractures and 7% of non-fractures were reclassified for the tibia, giving an overall net reclassification improvement value of 18% (95% CI 11–26). For the radius, reclassifications were seen for 7% of fractures and 14% of non-fractures, giving an overall net reclassification improvement value of 21% (95% CI 13–30; appendix). When we compared μFEA failure load with femoral neck aBMD alone, 14% of fractures and 3% of non-fractures were reclassified events (overall 17%, 95% CI 7–28) for the tibia, and 17% and 2%, respectively (overall 19%, 8–29) for the radius.

	Area under curve (95% CI)*	p value
FN aBMD†		
Tibia (n=6487)		
FN aBMD	0·665 (0·643–0·687)	Reference
FN aBMD plus cortical area, cortical vBMD, trabecular number, trabecular thickness	0·676 (0·653–0·698)	0·0059
Radius (n=6052)		
FN aBMD	0·670 (0·646–0·693)	Reference
FN aBMD plus cortical vBMD, trabecular number, and trabecular thickness	0·688 (0·665–0·711)	0·0005
FRAX‡		
Tibia (n=6472)		
FRAX	0·655 (0·633–0·676)	Reference
FRAX plus cortical area, cortical vBMD, trabecular number, trabecular thickness	0·669 (0·647–0·691)	0·0095
Radius (n=6035)		
FRAX	0·657 (0·634–0·679)	Reference
FRAX plus cortical vBMD, trabecular number, and trabecular thickness	0·683 (0·659–0·706)	0·0002

FN=femoral neck. aBMD=areal bone mineral density. vBMD=volumetric bone mineral density. FRAX=Fracture Risk Assessment Tool. *C statistic. †Models adjusted for age, sex, cohort, weight, and height. ‡Models adjusted for cohort; FRAX score incorporates age, sex, height, and weight.

Table 3: **Predictive accuracy of models including high-resolution peripheral quantitative CT bone indices compared with models including FN aBMD or FRAX alone**

	Area under the curve* (95% CI)	p value
Tibia (n=4143)		
FN aBMD	0·683 (0·654–0·712)	Reference
FN aBMD plus failure load†	0·697 (0·669–0·725)	0·0065
Radius (n=3845)		
FN aBMD	0·687 (0·657–0·717)	Reference
FN aBMD plus failure load†	0·702 (0·672–0·731)	0·0183

All models are adjusted for age, sex, cohort, weight, and height. FN=femoral neck. aBMD=areal bone mineral density. *C statistic. †Estimated by linear microfinite element analysis.

Table 4: **Predictive accuracy of models including tibia and radius failure load compared with femoral neck aBMD alone**

Discussion

Many fractures occur in individuals not identified as being at high risk by BMD testing, clinical risk factors, or both. In this large international cohort of more than 7000 women and men with 765 incident fractures, followed up for an average of 4·6 years, we found that trabecular and cortical bone density and microstructure, as well as estimated failure load measured at the peripheral skeleton, predict incident fractures independently of femoral neck aBMD and FRAX.

Our findings are consistent with those of previous cross-sectional studies and prospective studies in smaller cohorts,[11–15] which have shown associations between fractures and cortical and trabecular bone measures at the distal radius and tibia. Consistent strong associations with incident fracture in the prospective studies have included trabecular bone density at the distal radius,[14,15]

cortical area at the distal radius and distal tibia,[11,14] and stiffness or μFEA failure load.[11,14,15] We also found that failure load was the strongest predictor of incident fracture at the tibia and radius, and that this association was independent of femoral neck aBMD and FRAX. μFEA failure load intrinsically includes information on bone structure and density, which is why it performed as well as or better than the best combination of individual parameters. The best set of fracture predictors included cortical volumetric density, trabecular number, and trabecular thickness at the radius and these variables plus cortical area at the tibia, which is consistent with previous work.[11,14] Furthermore, these HR-pQCT variables and the μFEA failure load improved prediction of incident fracture beyond femoral neck aBMD and FRAX.

In contrast to some previous cross-sectional studies,[10,33] we found no strong association between cortical porosity and incident fracture. This discrepancy could be due to differences in fracture outcomes: previous studies used forearm[33] or hip[10] fracture, whereas we assessed any fracture and major osteoporotic fracture. Another explanation might be the use of different approaches to assess cortical porosity. In the BoMIC consortium, the threshold-based method for porosity assessment in the Scanco software was used, whereas the density-based method in the Strax software[34] was used in the previous case-control studies.[8,33] Importantly, both approaches are strongly associated (r^2>0·93) with cortical porosity measured by the gold standard, synchrotron micro-computed tomography.[35] Porosity is consistently underestimated by the threshold-based method, whereas it is consistently overestimated by the density-based method. In addition, the algorithms used to delineate the cortical region are markedly different between the Scanco and Strax software, making direct comparisons across studies difficult.

Our results have important clinical implications. Notably, most participants had femoral neck DXA aBMD T scores in the osteopenic or normal range. Thus, assessment of bone microstructure is likely to be useful for this important group of people who might not otherwise be identified as being at risk of fracture by standard clinical testing. We focused on the ability of HR-pQCT to predict fracture independently of DXA aBMD at the femoral neck, which is the site used for clinical diagnosis of osteoporosis and determination of fracture risk. However, the femoral neck is distinct from the sites of the HR-pQCT measurements. When we adjusted for DXA aBMD at the same ultradistal radius site as the HR-pQCT measurements, trabecular vBMD and trabecular number remained independent predictors of fracture, which suggests that bone microarchitecture in the peripheral skeleton provides information about skeletal fragility not captured by DXA aBMD. The sample size for this analysis, however, was reduced due to missing data in some cohorts, and this interpretation should be viewed with caution.

This study has several strengths. First, we included a large non-clinical sample of women and men from several countries, although these were limited to Europe and North America and cohorts included few non-white individuals. Second, the active surveillance and adjudication of fractures by all cohorts was another important strength of this study and enabled evaluation of all incident and major osteoporotic fracture. Third, all the cohorts used similar, standardised methods for data collection, including HR-pQCT and DXA imaging, FRAX calculation, and assessment of confounders, such as measured height and weight. We standardised femoral neck aBMD values with published equations to remove possible systematic differences between DXA systems.[30] We cannot, however, entirely rule out heterogeneity in data collection across study sites. The prospective design of this study helps to ensure that heterogeneity or errors in measurement were unrelated to fracture outcomes and, therefore, would have led to underestimation of associations. The information obtained by questionnaire used to calculate FRAX scores might also have been subject to error, for example through under-reporting of smoking and alcohol consumption by respondents. Thus, adjustment for FRAX could have been inadequate for such individuals, possibly resulting in overestimation of associations between HR-pQCT and fracture. Under-reporting of risk factors, however, is likely to occur in clinical practice.

Our study had some limitations. First, all HR-pQCT scans were acquired at a fixed distance from the endplate of the distal radius or tibia, meaning that the anatomy of the skeletal regions measured may have differed slightly due to the individual's limb length, which could have obscured differences in bone density and morphology. A second limitation is that we did not cross-calibrate the different HR-pQCT devices used in this study, which could have led to an underestimation of associations. The central coordinating site reviewed the HR-pQCT data from each cohort for quality control, and all sites used one type of scanner, the same protocol for scan acquisition, and the same analysis method. Third, μFEA was not done in all cohorts. Nevertheless, despite relatively wide CIs, failure load was the strongest predictor of fracture. Furthermore, we found no difference in the mean age or fracture incidence between participants with and without data on failure load, although femoral neck T score was lower in those with than without missing failure load values (–1·35 *vs* –1·12 for radius μFEA and –1·32 *vs* –1·15 for tibia μFEA; data not shown). This difference might mean that we have underestimated associations between failure load and fracture incidence.

In summary, we showed that peripheral measurements of cortical and trabecular bone density, microstructure, and strength are associated with incident fracture independently of femoral neck DXA BMD and FRAX. Notably, most fractures occurred in individuals not

shown to have osteoporosis by BMD T scores but in whom deficits in bone microstructure were found with HR-pQCT. Although HR-pQCT is not widely available, our findings suggest that expansion of the clinical use of this technique and the development of alternative technologies to assess cortical and trabecular bone structure and strength could be beneficial. We have provided the groundwork to develop new models for fracture prediction, thereby improving risk stratification and reducing the public health burden of osteoporosis.

Contributors

EJS, SD, DPK, and MLB designed and did the study. All authors collected data. EJS, HX, SD, DPK, and MLB analysed the data and EJS, SB, EB, PS, CO, SD, DPK, and MLB interpreted the data. EJS and MLB drafted the manuscript, content revisions were provided by EJS, SB, EB, PS, CO, SD, DPK, and MLB, and all authors approved the final version. EJS takes responsibility for the integrity of the data analysis.

Declaration of interests

SB is the cofounder of Numerics88 Solutions, which provides estimates of bone strength from HR-pQCT images. JA has received grants and personal fees from Amgen, Eli Lilly, and Merck, grants from Actavis, and personal fees from Agnovis. RC has received grants and personal fees from Amgen, Chugai, and Merck and personal fees from Abbvie, BMS, Lilly, Pfizer, Sanoz, and UCB. DAH has received grants and personal fees from Amgen and grants from Pure North S'Energy Foundation. ML has received personal fees from Amgen, Consilient Health, Lilly, Meda, Radius Health, Renapharma, and UCB Pharma. RR has received personal fees from CNIEL, Danone, Pfizer, Radius Health, and Sandoz. BVR has received personal fees from Scanco Medical. DPK has received personal fees from Springer. All other authors declare no competing interests.

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