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Women with fracture, unidentified by FRAX, but identified by cortical porosity, have a set of characteristics that contribute to their increased fracture risk beyond high FRAX score and high cortical porosity

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ABSTRACT

The Fracture Risk Assessment Tool (FRAX) is widely used to identify individuals at increased risk for fracture. However, cortical porosity is associated with risk for fracture independent of FRAX and is reported to improve the net reclassification of fracture cases. We wanted to test the hypothesis that women with fracture who are unidentified by high FRAX score, but identified by high cortical porosity, have a set of characteristics that contribute to their fracture risk beyond high FRAX score and high cortical porosity. We quantified FRAX score with femoral neck areal bone mineral density (FN aBMD), and femoral subtrochanteric architecture, in 211 postmenopausal women aged 54–94 years with non-vertebral fractures, and 232 fracture-free controls in Tromsø, Norway, using StrAx software. Of 211 fracture cases, FRAX score > 20% identified 53 women (sensitivity 25.1% and specificity 93.5%), while cortical porosity cut-off > 80th percentile identified 61 women (sensitivity 28.9% and specificity 87.9%). The 43 (20.4%) additional fracture cases identified by high cortical porosity alone, had lower FRAX score (12.3 vs. 26.2%) than those identified by FRAX alone, they were younger, had higher FN aBMD (806 vs. 738 mg/cm^2), and fewer had a prior fracture (23.3 vs. 62.9%), all $p < 0.05$. They had higher cortical porosity (48.7 vs. 42.1%), thinner cortices (3.75 vs. 4.12 mm), lower cortical and total volumetric BMD (942 vs. 1053 and 586 vs. 699 mg HA/cm^3), larger medullary and total cross-sectional areas (245 vs. 190 and 669 vs. 593 mm^2), and higher cross-sectional moment of inertia (2619 vs. 2388 cm^4) all $p < 0.001$. When the fracture cases and controls with high cortical porosity were compared, cases had higher cortical porosity, lower cortical vBMD, lower total vBMD, smaller cortical CSA/Total CSA, larger medullary CSA and larger total CSA than controls (all $p \leq 0.05$). Thus, fracture cases, unidentified by FRAX, but identified by cortical porosity, had an architecture where the positive impact of larger bone size did not offset the negative effect of thinner cortices with increased porosity. A measurement of cortical porosity may be a marker of other characteristics that capture additional fracture risk components, not captured by FRAX.

1. Introduction

The Fracture Risk Assessment Tool (FRAX) is widely used in many countries and has improved fracture risk prediction compared to areal bone mineral density (aBMD) alone [1–3]. Despite of the inclusion of several well-known risk factors for fracture, this tool has limitations in terms of lack of sensitivity [4,5]. For this reason, there are ongoing discussions concerning which of the included risk factors may not be needed, as well as which factors could be added to FRAX to improve the fracture prediction [3]. This is an important discussion because low aBMD is one of the key components of high FRAX score, while a majority of those individuals who suffer fractures have either normal or only slightly reduced aBMD. Many bone features contribute to bone strength, such as the bone architecture and geometry, which could aid finding those who do not have the traditional risk factors such as older age and low aBMD [6,7]. A larger size is important for bone strength,

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because the resistance to bending increases to the fourth power of its radius [8]. Moreover, deterioration of both the cortical as well as the trabecular architecture compromises bone strength [8,9]. However, in an experimental study, which examined the contribution of cortical versus trabecular bone using biomechanical testing, trabecular bone contributed to only 7% of bone strength in the femoral neck [10]. Trabecular bone score can be used in the FRAX calculation, but it results in only a modest improvement of fracture risk prediction [3,11]. Cortical porosity is a potential risk factor for fracture as cortical bone constitute 80% of the skeleton [12], and contribute over 90% to bone strength [10], still, cortical porosity or other cortical bone parameters are not included in the FRAX.

Several cross-sectional studies have reported that increased cortical porosity assessed using high-resolution peripheral quantitative computed tomography (HR-pQCT) and clinical CT technology, is associated with prevalent fracture in women and men [13–17]. In contrast, no association was confirmed between cortical porosity at distal tibia and fracture risk in a prospective study of elderly men using HR-pQCT software [18]. In another study using HR-pQCT and StrAx software, cortical porosity of the inner transitional zone at the ultra-distal radius was associated with incident fracture in postmenopausal women independent of femoral neck (FN) aBMD and FRAX score, but only marginally after adjustment for ultra-distal radius aBMD [19]. Our research group has previously reported that increased cortical porosity at the proximal femur was associated with fracture independent of FN aBMD and FRAX [15,20]. Using a cortical porosity threshold > 80th percentile identified 20% additional fracture cases who were unidentified by FRAX, and improved the net reclassification of fracture cases [20]. This suggests that a measurement of cortical porosity captures other important skeletal properties not captured by the FRAX score. The reasons why some women are identified by FRAX, while others are identified by a measurement of cortical porosity is not clear. To the best of our knowledge, no previous study have reported the characteristics of those additional individuals with fractures who are identified by cortical porosity independently of FRAX. We reanalyzed the data, and explored the differences in clinical characteristics, cortical architecture, bone geometry and a strength estimate between the women with fracture identified by high FRAX score alone, those identified by a measurement of high cortical porosity alone, those who were unidentified by either, and control groups who had the same criteria as each of the groups of cases. We wanted to test the hypothesis that women with fracture who are unidentified by high FRAX score, but identified by high cortical porosity, have a set of characteristics that contribute to their fracture risk beyond high FRAX score and high cortical porosity.

2. Materials and methods

2.1. Study population

The Tromsø Study is a single-center, population-based study in Northern Norway, which conducted six surveys between 1974 and 2008 [21]. During the Tromsø 4 survey in 1994–95, 37,558 eligible inhabitants in Tromsø over 24 years old were invited to participate, and 27,158 (72%) agreed. Within these participants, all nonvertebral fractures that occurred between January 1, 1994 and January 1, 2010 were registered from the University Hospital of North Norway, Tromsø x-ray archives [22]. Participants with a vertebral fracture were not included in this x-ray based fracture registry, as few of them came to the hospital for an x-ray.

In 2011 we designed a nested case-control study and identified 1250 women from the x-ray-based fracture registry that suffered at least one fracture of the hip, wrist, or proximal humerus after the age of 50 years [15,20,23–25]. We invited all 760 women who were still alive and living in Tromsø. All women who were willing to participate had a pre-screening phone call to determine whether they were eligible for participation in accordance with the inclusion and exclusion criteria. Those who were premenopausal, received bisphosphonates, or had hip prostheses or metal screws in the hip region were excluded from the study. Since metal on one hip can create noise in the CT images on both sides, many women with a hip fracture could not be included unless they had the metal removed. After screening, 264 fracture cases were included in the study [15,20,23,24]. Age-matched, fracture-free women, who were within the same 5-year age groups, were randomly selected from the Tromsø 4 participants, and 1186 were invited. After a pre-screening phone call to determine whether they were eligible and fracture-free, 260 controls were included. Of these 524 participants, we excluded 15 women who were currently receiving hormone replacement therapy and 66 women due to motion artifacts during CT scanning. This left 443 women included in the final analyses: 232 fracture-free controls and 211 fracture cases (4 hip, 181 wrist, and 26 proximal humerus). The median time since last fracture was 6.6 years (range, 1–25). All variables included in the analysis were based on information obtained at the time of study enrollment between November 2011 and January 2013, CT scanning was performed between March 2012 and January 2013. All participants provided written informed consent. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK Sør-Øst, 2010/2282) and was conducted in accordance with the World Medical Association Declaration of Helsinki.

2.2. Variables and measurements

At enrollment of the study, the participants filled in a questionnaire that included information concerning all fractures after the age of 50 years (number and type of fracture), diseases, use of medication and lifestyle. Height and weight were measured while wearing light clothing and without shoes. Body mass index (BMI) was calculated as weight/height^2. FN aBMD was measured using dual-energy x-ray absorptiometry (DXA) (GE Lunar Prodigy, Lunar Corporation, Madison, WI, USA) and the coefficients of variation (CV) was 1.7%.

We entered the data collected at enrollment into the online country-specific FRAX algorithm for Norway to calculate the individual 10-year probability of a major osteoporotic fracture (http://www.shef.ac.uk/FRAX/). An age of 90 years was entered into the calculation tool in women older than 90 years of age, and we included FN aBMD in the calculation of FRAX score [20]. The index fractures used as inclusion criteria for this study were not included as a “previous” fracture in the calculation of the FRAX score, because the aim was to assess the 10-year probability of fracture before the event, not the probability of fracture after this event [14,15]. Whereas the “previous fractures” (before the index fracture) and “subsequent fractures” (after the index fracture) were used equally in the calculation of FRAX score [20].

CT scans (Siemens Somatom Sensation 16, Erlangen, Germany) of the non-dominant hip were performed at the Department of Radiology at the University Hospital of North Norway [15]. The CT machine had an in-plane resolution of 0.74 mm and the slice thickness was set at 0.6 mm. The hip was scanned from just above the femoral head to 2 cm below the lesser trochanter, and the exposure dose of radiation was ~1.5 mSv [15]. CT scans of the hip were performed at 120 kV, with a pitch of 0.75, using 90 mA, and reconstructed using a fixed field of view at 120 mm [26]. Quality control was carried out by scanning a phantom containing rods of hydroxyapatite (QRM Quality Assurance in Radiology and Medicine GmbH, Moehrendorf, Germany). The CT images were sent to Melbourne, Australia, and analyzed by collaborators, who were blinded to the fracture status, using the StrAx software (StraxCorp Pty Ltd., Melbourne, Australia). As cortices are thin at the most proximal femur (femoral head, neck and trochanter), analyses were confined to a 3.7 mm subtrochanteric region of interest (ROI) with thicker cortices, which started at the tip of the lesser trochanter [15,27].

The StrAx software is a non-thresholding method that automatically selects attenuation profile curves and segments the bone within the ROI into its compartments, the compact-appearing cortex, outer (OTZ) and

inner transitional zone (ITZ), and trabecular compartment [28]. This was achieved by quantification of the attenuation produced by background (i.e., muscle) and fully mineralized bone matrix, which has a density of 1200 mg hydroxyapatite ((HA)/cm^3) and assigned a value of 100% [27,28]. Voxels that were completely empty and had an attenuation equivalent to background were 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. Once deposited, osteoid is rapidly mineralized to become 'bone', reaching 80% of full mineralization (1200 mg HA/cm^3) within a few days. Voxels with attenuation values of 80% are unlikely to contain a pore or part of a pore, because porosity results in voxel attenuation values < 80% of the maximum. Variations in attenuation within 80% to 100% of full mineralization are likely to reflect heterogeneity in secondary mineralization of the matrix, thus these voxels are excluded from the calculation of porosity [28]. Voxels with attenuation < 80% may contain a pore or part of a pore [28].

Porosity within the total cortex and each cortical compartment was quantified automatically throughout the ROI using the StrAx software [15]. The porosity quantified by this algorithm is the average proportion of emptiness within each voxel or the fraction of the bone that is void, with CV of 0.3–2.3% [15]. StrAx quantifies porosity in low-resolution images [15,27], as in high-resolution images [13,28,29], even though pores are not visible. It is a density-based, indirect measure of porosity, and the size and number of pores are not determined [15,28,30]. Of the total cortex at this subtrochanteric site, 70.0% was compact-appearing cortex, while 22.3% and 11.7% was OTZ and ITZ, respectively. The agreement (R^2) between CT and HR-pQCT ranged from 0.86 to 0.96 for quantification of porosity (ranging from 40 to 95%), at the same femoral subtrochanteric site [15,27]. The StrAx software quantifies porosity as a fraction of void, regardless of size of the pores, and indirectly captures porosity produced by large and small pores. It is more inclusive than traditional methods by capturing porosity of the compact cortex and the TZ, and by taking into account the partial volume effect by including void within completely empty and partly empty voxels, and the porosity is therefore higher than what is reported using other methods [27,28,30].

2.3. Statistical analyses

Sensitivity and specificity for fracture were explored at selected thresholds for FRAX score above 15%, 20%, and 25%, and cortical porosity above the 75th, 80th, and 90th percentile. We chose specificity above 85% as a reasonable criterion for selection of thresholds for each of the variables for further analysis [20]. We present mean and standard error of the mean (SE) for the following variables: FRAX score, age, height, weight, BMI, FN aBMD, hours of physical activity per week, the femoral subtrochanteric cortical porosity, thickness, volumetric BMD (vBMD) and cross-sectional area (CSA), and cortical CSA as a proportion of the total CSA (cortical CSA/total CSA), trabecular bone volume per tissue volume (BV/TV), medullary CSA, total vBMD and CSA and the bone strength estimate cross-sectional moment of inertia (CSMI). We present the number and proportion of women with a prior fracture, parental hip fracture history, rheumatoid arthritis, oral corticosteroid use, and currently smokers in six groups.

Group 1: 35 fracture cases with high FRAX score (threshold > 20%), without high cortical porosity (threshold ≤ 80th percentile). Group 2: 10 controls with high FRAX score, without high cortical porosity. Group 3: 43 fracture cases without high FRAX score (≤ 20%), with high cortical porosity (> 80th percentile). Group 4: 23 controls without high FRAX score, with high cortical porosity. Group 5: 115 fracture cases unidentified by either. Group 6: 194 controls without either high FRAX score or high cortical porosity. The characteristics of the women in each of the groups were compared using age-adjusted analysis of variance, and the bone parameters were compared after additionally adjustment for FN aBMD, height and weight. We used SAS Software, v9.4 (SAS Institute Inc., Cary, NC, USA) and $p \leq 0.05$ was considered significant.

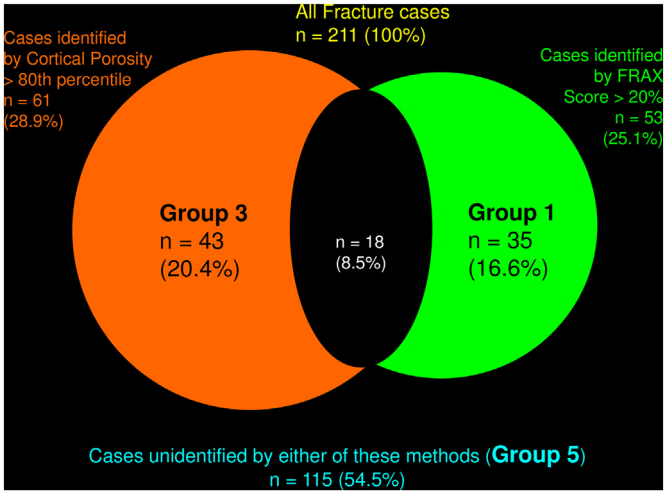

Fig. 1. Fractures cases identified by high cortical porosity alone, high Fracture Risk Assessment Tool (FRAX) score alone, the overlap, and cases unidentified by either of these measurements.

3. Results

3.1. Sensitivity and specificity for fracture

Of all 211 fracture cases, FRAX score > 20% identified 53 women, with a sensitivity of 25.1% and specificity of 93.5%, while a measurement of femoral subtrochanteric cortical porosity with cut-off > 80th percentile identified 61 women, with a sensitivity of 28.9% and specificity of 87.9% (Fig. 1). Of 211 fracture cases, 35 (16.6%) (Group 1) were identified only by high FRAX score, and 43 (20.4%) (Group 3) were identified only by high cortical porosity. There was an overlap for 18 (8.5%) women with fracture who had both high FRAX score and high cortical porosity, and 115 (54.5%) (Group 5) fracture cases were unidentified by either. Of 232 fracture-free controls, 10 (4.3%) (Group 2) had FRAX score > 20% and cortical porosity ≤ 80th percentile, 23 (9.9%) (Group 4) had FRAX score ≤ 20% and cortical porosity > 80th percentile, and 194 (83.6%) (Group 6) had FRAX score ≤ 20% and cortical porosity ≤ 80th percentile.

3.2. Characteristics of fracture cases identified by high FRAX score alone

Fracture cases identified by high FRAX score alone, had a higher FRAX score (26.2 vs. 12.3%), were 4 years older (71.7 vs. 67.6), had 8.4% lower FN aBMD (738 vs. 806 mg/cm^2), and more had a prior fracture (22 vs. 10%) and a parental history of hip fracture (16 vs. 4%) compared to those identified by high cortical porosity alone (Group 1 vs. Group 3, all $p < 0.05$, Table 1 and Fig. 2). Similar differences were found between fracture cases identified with high FRAX score and cases unidentified by either (Group 1 vs. Group 5). No differences were found between fracture cases and fracture-free controls with high FRAX score alone (Group 1 vs. Group 2).

3.3. Characteristics of fracture cases identified by high cortical porosity alone

Women with fracture who were identified by high cortical porosity alone, had 15.7% higher cortical porosity (48.7 vs. 42.1%), 9.0% thinner cortices (3.75 vs. 4.12 mm), 10.5% lower cortical vBMD (942 vs. 1053 mg HA/cm^3), 16.2% lower total vBMD (586 vs. 699 mg HA/cm^3), 28.9% larger medullary CSA (245 vs.190 mm^2), 12.8% larger total CSA (669 vs. 593 mm^2), and 9.7% higher CSMI (2619 vs.

Table 1
Characteristics of fracture cases identified by high FRAX score or high cortical porosity alone, unidentified by either, and controls.

	FRAX score > 20%		Porosity > 80th percentile		Unidentified by either methods	
Groups (Gr.) of cases and controls	Gr. 1 cases	Gr. 2 controls	Gr. 3 cases	Gr. 4 controls	Gr. 5 cases	Gr. 6 controls
n	35	10	43	23	115	194
FRAX score (%)	26.2 (1.2)[c,f]	24.0 (0.9)	12.3 (0.6)	11.4 (0.7)	11.2 (0.3)[i]	9.7 (0.3)
Age (years)	71.7 (1.3)[a,f]	74.9 (1.3)	67.6 (1.1)	67.7 (1.0)	66.6 (0.7)	67.9 (0.5)
Height (cm)	162.3 (1.2)	160.5 (2.3)	164.1 (0.8)	164.3 (0.9)	162.8 (0.6)[h]	160.8 (0.5)
Weight (kg)	69.7 (1.3)	67.1 (4.0)	70.3 (1.8)	72.9 (2.1)	69.3 (1.0)	69.9 (0.8)
Body mass index (BMI) ((kg/m^2)	26.6 (0.6)	26.2 (1.7)	26.1 (0.7)	27.0 (0.8)	26.1 (0.4)	27.1 (0.3)
Femoral neck aBMD (mg/cm^2)	738 (11.9)[b,f]	733 (27.1)	806 (12.7)	809 (15.4)	825 (9.1)[i]	877 (7.8)
Physical activity (h/week)	2.2 (0.2)	2.3 (0.5)	2.8 (0.3)	2.7 (0.4)	2.7 (0.2)	2.5 (0.1)
History of previous fracture, n (%)	22 (62.9)[c,f]	0	10 (23.3)	0	18 (15.7)	0
Parental hip fracture history, n (%)	16 (45.7)[c,f]	5 (50.0)	4 (9.3)	4 (17.4)	12 (10.4)	25 (12.9)
Currently smoking, n (%)	6 (17.1)	2 (20.0)	7 (16.3)	3 (13.0)	14 (12.2)	19 (9.8)
Rheumatoid arthritis, n (%)	5 (14.3)[a,e]	2 (20.0)	2 (4.7)	1 (4.3)	3 (2.6)	5 (2.6)
Oral corticosteroid use, n (%)	6 (17.1)[c,f]	2 (20.0)	1 (2.3)	0	1 (0.9)	0
Femoral subtrochanteric parameters						
Cortical porosity (%)	42.1 (0.4)[c]	41.0 (0.8)	48.7 (0.4)[f,h]	47.3 (0.2)	41.4 (0.2)	40.9 (0.2)
Cortical thickness (mm)	4.12 (0.08)[c]	4.34 (0.17)	3.75 (0.09)[f]	3.96 (0.08)	4.27 (0.04)	4.42 (0.04)
Cortical vBMD (mg HA/cm^3)	1053 (6.7)[c]	1071 (13.0)	942 (6.6)[f,h]	967 (4.1)	1065 (3.8)	1073 (3.2)
Cortical CSA (mm^2)	403 (6.4)[b]	408 (9.8)	424 (5.8)	430 (6.6)	410 (3.7)	417 (2.9)
Cortical CSA/total CSA	0.68 (0.01)[c,d]	0.70 (0.02)	0.64 (0.01)[f,g]	0.67 (0.06)	0.71 (0.005)	0.73 (0.003)
Trabecular BV/TV (%)	0.24 (0.03)	0.17 (0.05)	0.36 (0.04)[d]	0.43 (0.07)	0.24 (0.02)	0.26 (0.02)
Medullary CSA (mm^2)	190 (7.2)[c]	172 (12.8)	245 (10.5)[f,g]	213 (5.4)	169 (4.3)	156 (2.7)
Total bone vBMD (mg HA/cm^3)	699 (12.5)[c,d]	736 (23.2)	586 (12.6)[f,h]	633 (8.2)	743 (7.9)	769 (5.7)
Total bone CSA (mm^2)	593 (10.0)[c]	580 (10.9)	669 (12.2)[f,g]	644 (8.8)	578 (5.9)	573 (4.2)
Cross-sectional moment of inertia	2388 (56)[c]	2335 (51)	2619 (56)[f]	2570 (53)	2332 (31)	2335 (23)

Values are mean (standard error of the mean) or number (%). FRAX = Fracture Risk Assessment Tool for calculation of the 10-year probability of a major osteoporotic fracture; aBMD = areal bone mineral density; vBMD = volumetric BMD; HA = hydroxyapatite; CSA = cross sectional area; BV/TV = bone volume per tissue volume. Analysis of variance is used for comparisons of groups, all comparisons are age-adjusted, and comparisons of bone traits are additionally adjusted for aBMD, height and weight.

[a] $p \le 0.05$.
[b] $p \le 0.01$.
[c] $p \le 0.001$ compared to group 3.
[d] $p \le 0.05$.
[e] $p \le 0.01$.
[f] $p \le 0.001$ compared to group 5.
[g] $p \le 0.05$.
[h] $p \le 0.01$.
[i] $p \le 0.001$ compared to controls.

2388 cm^4), compared to cases identified by high FRAX score alone (Group 3 vs. Group 1, all $p < 0.001$, Table 1, Fig. 3). Similar differences were found between fracture cases identified with high cortical porosity and cases unidentified by either (Group 3 vs. Group 5). When we compared fracture cases and fracture-free controls with high cortical porosity alone, cases had higher cortical porosity, lower cortical vBMD, lower total vBMD, smaller cortical CSA/total CSA, larger medullary CSA and larger total CSA than controls after adjustment for age, height, weight and aBMD (Group 3 vs. Group 4, all $p \le 0.05$).

3.4. Characteristics of fracture cases unidentified by either high FRAX or cortical porosity

When we compared fracture cases and controls who were unidentified by either high FRAX or cortical porosity, cases had higher FRAX score, were taller and had lower FN aBMD than controls (Group 5 vs. Group 6, all $p < 0.01$). Otherwise, fracture cases unidentified by either had significantly thinner cortices, smaller cortical CSA, smaller cortical CSA/total CSA, larger medullary CSA and lower total vBMD than controls before ($p < 0.05$) but not after adjustment for FN aBMD.

4. Discussion

We report that fracture cases unidentified by FRAX but identified by cortical porosity, differed from cases identified by FRAX, beyond high FRAX score and cortical porosity. Cases identified by cortical porosity alone, had lower FRAX score, were younger, with higher FN aBMD, fewer had a prior fracture and parental history of hip fracture, and they had a larger medullary cavity and bone size, thinner and more porous cortices at the femoral subtrochanteric site, than cases identified by FRAX alone. When we compared fracture cases and controls who had high cortical porosity, cases still had higher cortical porosity, lower cortical and total vBMD, smaller cortical CSA/total CSA (relatively thinner cortices), larger medullary and total bone area than controls. From these results we infer that a measurement of cortical porosity captured a set of additional fracture risk components, not captured by FRAX or porosity.

As expected, fracture cases identified by FRAX were older, with lower FN aBMD, and more had a prior fracture, as these are the key components of the FRAX tool. We further confirmed that FRAX captured the risk factors related to diseases as rheumatoid arthritis and oral use of corticosteroids. Still, only 25% of the fracture cases were identified by FRAX, and several other bone traits reflecting risk components of the multifactorial condition bone fragility seem not to be well captured by this tool [5]. A proportion of only 8.5% of the fracture cases were identified by both FRAX and cortical porosity in this study. This small overlap suggests that there probably are major differences between the characteristics of these two groups of fracture cases. In addition, cortical porosity improved the net reclassification of fracture cases when cortical porosity was added to FRAX, which support the notion that cortical porosity makes an important and independent contribution to identification of fracture risk [20].

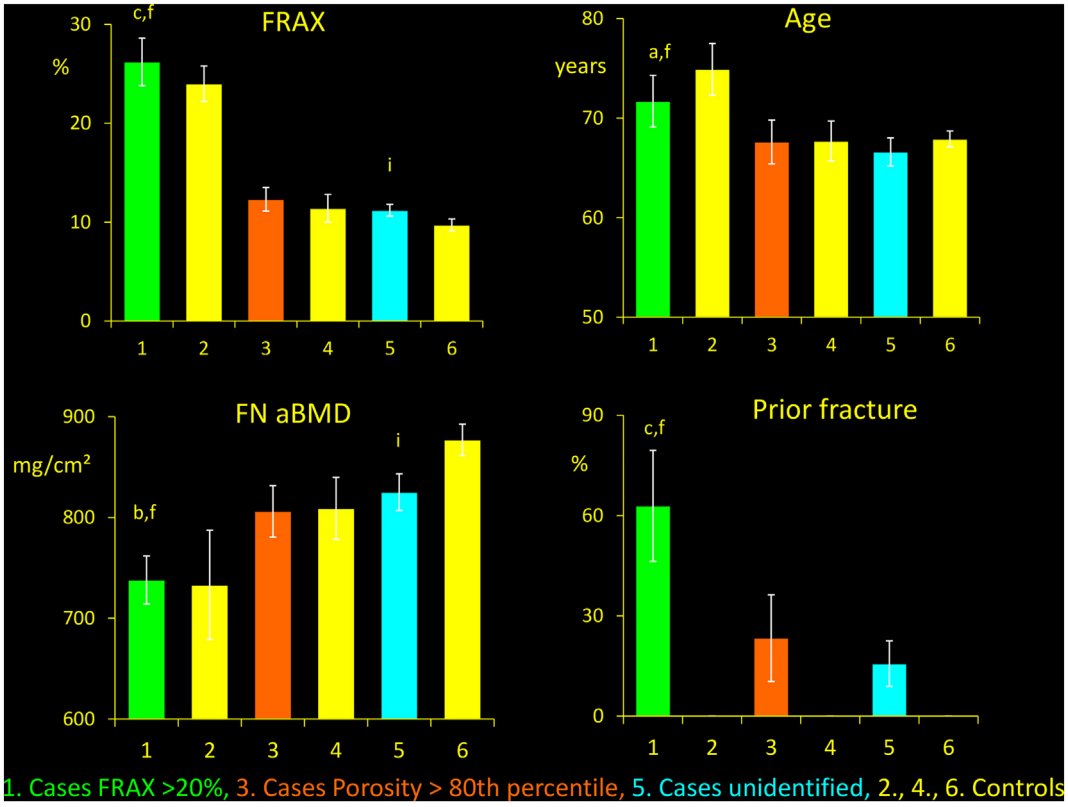

Fig. 2. Fracture Risk Assessment Tool (FRAX) score, age, femoral neck areal bone mineral density (FN aBMD) and proportion with a prior fracture in six groups. Group 1: fracture cases with high FRAX score (> 20%), without high cortical porosity (≤ 80th percentile). Group 2: controls with high FRAX score, without high cortical porosity. Group 3: fracture cases without high FRAX score (≤ 20%), with high cortical porosity (> 80th percentile). Group 4: controls without high FRAX score, with high cortical porosity. Group 5: fracture cases without either. Group 6: controls without either.

Of the 75% of fracture cases who were unidentified by FRAX, 20% were identified by cortical porosity. They did not have the characteristic risk factors identified by FRAX, but they had a set of bone parameters that differed from those identified by FRAX. In addition to high cortical porosity, they had thinner cortices, both are well-known risk factors for fracture [31]. They had a larger total bone CSA and increased CSMI, which would be expected to reduce the risk for fracture [8,9]. The increased risk for fracture in these women, suggest that the strength gained by larger bone size, did not offset the strength lost by the thinner cortices with higher cortical porosity [24]. Larger bone size is associated with higher cortical porosity [13,32] and taller individuals who on average have longer and wider bones, have increased risk for fracture [33,34]. The increased porosity combined with relatively thinner cortices, may partly explain why taller individuals, despite of their larger bone size, have increased risk for fracture [13,32].

Fracture cases identified by high cortical porosity, had lower total bone vBMD, so their larger bones were more empty, because they had thinner cortices with higher porosity, smaller cortical CSA/total CSA, and thus larger medullary CSA/total CSA and larger medullary CSA, than other fracture cases and controls. Our research group has reported that women with fracture had increased bone turnover markers, and the increased levels of bone turnover markers were associated with higher cortical porosity, thinner cortices, larger marrow cavity and larger bone size [24]. Bone turnover occurs on all endosteal surfaces; intracortical, endocortical and trabecular surfaces [12]. Increased bone turnover i) on the intracortical surfaces results in larger pores and increased porosity within the cortical compartment, ii) on the endocortical surfaces results in a larger medullary cavity and thinning of the cortex, and iii) on the trabecular surfaces it results in thinning and loss of trabeculae [35,36]. All these changes result in reduced bone strength [6,12]. A measurement of cortical porosity may be a marker for this whole set of the above-mentioned bone traits, and it can be useful for identification of individuals at risk for fracture, beyond those traits that is captured by FRAX.

In women with fracture identified by high cortical porosity, the high porosity in the cortical bone may cause an important loss of strengths as it is located distant to the neutral axis, given the high stress on the outer part of the bone during a trauma [35]. This may partly explain their increased risk for fracture. Cortical bone microstructure, especially cortical porosity has a major impact on bone strengths [37,38]. An increase in porosity from 4 to 20% decrease the ability of bone to resist fracture by three-fold [39]. In addition, 70–80% of the variation in stiffness as examined in the femoral cortex, can be explained by changes in cortical porosity [38,40]. High cortical porosity can appear as giant pores in cross-sectional images, which decrease the ability of the cortex to withstand stress [41] and resist crack propagation especially under tensile loading [42,43]. Moreover, microcracks located near intracortical pores compromise fracture resistance [44].

Different genetic variants associated with cortical and trabecular bone traits are identified [45], and up to 80% of the variance in cortical and trabecular microarchitecture are determined by genetic factors [29]. The implication of those findings is that the heterogeneous pathophysiology behind bone fragility, is not only a result of age-related changes, but genetic variation that is established during growth early in life, and may contribute to fracture risk in younger age [35]. The fracture cases who were unidentified by either high FRAX or cortical porosity, had higher FRAX score than controls, they were taller and had lower FN aBMD. This confirmed that well-known risk factors operate below the chosen threshold for FRAX ≤ 20%. In addition, they may have other risk factors for fracture beyond those we have quantified in this study, or their fracture might have occurred due to the trauma involved during their fall.

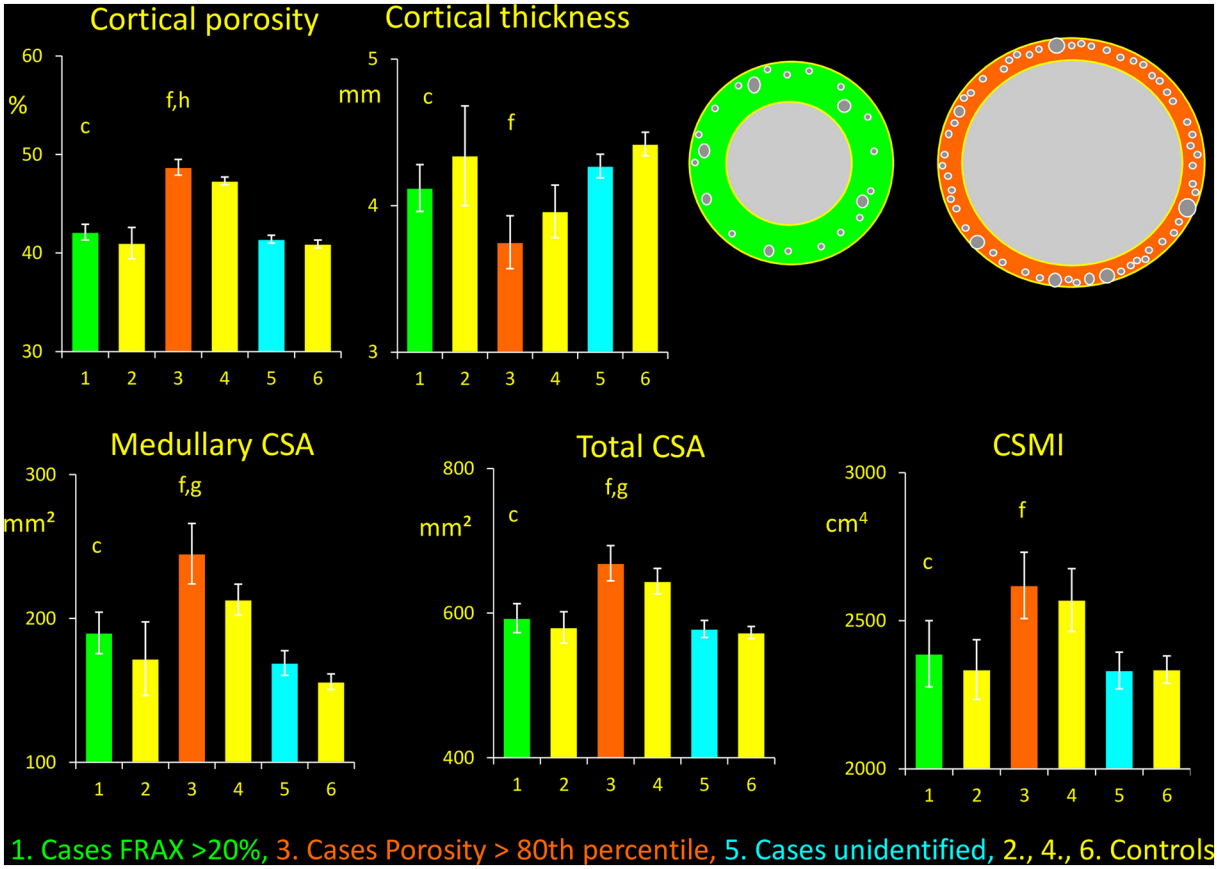

Fig. 3. Cortical porosity, cortical thickness, medullary and total cross-sectional area (CSA) and Cross-sectional Moment of Inertia (CSMI) at the femoral subtrochanteric site in six groups. Group 1: fracture cases with high FRAX score (> 20%), without high cortical porosity (≤ 80th percentile). Group 2: controls with high FRAX score, without high cortical porosity. Group 3: fracture cases without high FRAX score (≤ 20%), with high cortical porosity (> 80th percentile). Group 4: controls without high FRAX score, with high cortical porosity. Group 5: fracture cases without either. Group 6: controls without either.

The strength of this nested case-control study is that it is based on a general population, x-ray verified fractures, and the bone parameters are quantified at the proximal femur, a central site. The benefit and novelty of using this non-threshold based software lie in how it is different from traditional porosity measurements. It is more inclusive than traditional methods by capturing porosity not only of the compact cortex but also the TZ, and by taking into account the partial volume effect [28]. The study has several limitations. The index fracture occurred at a median of 6.6 years before the women had their measurements performed, and most of the women with hip fractures could not be included, as metal can generate noise in the CT images. The subtrochanteric region contained little trabecular bone, so its contribution to fracture risk could not be evaluated, and StrAx software is vulnerable to motion artifact. Moreover, porosity produced by smaller pores may not be identified with the image resolution used in this study, and may have resulted in a small error in the quantification of porosity [27]. Routine CT scanning of the proximal femur is not feasible in clinical practice to screen for fracture risk because of the high dose of radiation involved due to the large amount of soft tissue, but CT images obtained for other reasons as a hip fracture or osteoarthritis can be used.

In conclusion, fracture cases identified by high cortical porosity alone had a set of different characteristics compared to those identified by FRAX alone and compared to controls. In the relatively younger fracture cases unidentified by FRAX, the larger bone size did not offset the thinner cortices with higher cortical porosity. Such a set of characteristics is of interest for three reasons, firstly these women broke their bones without having the traditional risk factors as high age and low aBMD, secondly, they constitute a separate group of women that otherwise would not have been identified by calculation of FRAX, and thirdly, we have recently reported that cortical porosity improved the net reclassification of fracture cases [20]. This may explain why some women break their bone in relatively younger age, and may help identify those who are at risk for fracture before they have their first fracture. It demonstrate the challenges of predicting fracture at the individual level. A measurement of cortical porosity may be a marker of a combination of characteristics, which can identify additional women at risk for fracture, not captured by FRAX. Adding cortical porosity to FRAX may be of help to improve fracture risk assessment, not only for secondary, but also primary fracture prevention.

Disclosures

The authors have nothing to disclose.

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The Tromsø Study provided access to data. Staff at the Department of Research at the University Hospital of North Norway (UNN) recruited women, obtained consent and questionnaires, collected blood samples and performed DXA scanning. Staff at Department of Radiology and Department of Radiation, UNN performed CT scanning of the patients, organized the radiation procedures and the CT images, and StrAx Corp, Melbourne analyzed the CT images.

Authors' roles: Study concept, design, obtained funding and executed the study: RK, MO, ÅB. Statistical analysis: ÅB. Drafting manuscript: RK, MO, RV, ER, ÅB. Data interpretation and critical revision of the manuscript for important intellectual content, writing of the report and approval of the final version: RK, MO, RV, ER, ÅB. ÅB takes responsibility for the integrity of the data analyses.

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