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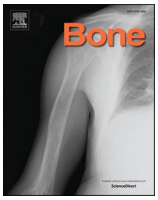

Cortical bone structure of the proximal femur and incident fractures

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ABSTRACT

Purpose: Fracture risk is most frequently assessed using Dual X-ray absorptiometry to measure areal bone mineral density (aBMD) and using the Fracture Risk Assessment Tool (FRAX). However, these approaches have limitations and additional bone measurements may enhance the predictive ability of these existing tools. Increased cortical porosity has been associated with incident fracture in some studies, but not in others. In this prospective study, we examined whether cortical bone structure of the proximal femur predicts incident fractures independent of aBMD and FRAX score.

Methods: We pooled 211 postmenopausal women with fractures aged 54–94 years at baseline and 232 fracture-free age-matched controls based on a prior nested case-control study from the Tromsø Study in Norway. We assessed baseline femoral neck (FN) aBMD, calculated FRAX 10-year probability of major osteoporotic fracture (MOF), and quantified femoral subtrochanteric cortical parameters: porosity, area, thickness, and volumetric BMD (vBMD) from CT images using the StrAx1.0 software. Associations between bone parameters and any incident fracture, MOF and hip fracture were determined using Cox's proportional hazard models to calculate hazard ratio (HR) with 95% confidence interval.

Results: During a median follow-up of 7.2 years, 114 (25.7%) of 443 women suffered one or more incident fracture. Cortical bone structure did not predict any incident fracture or MOF after adjustment for age, BMI, and previous fracture. Each SD higher total cortical porosity, thinner cortices, and lower cortical vBMD predicted hip fracture with increased risk of 46–62% (HRs ranging from 1.46 (1.01–2.11) to 1.62 (1.02–2.57)). After adjustment for FN aBMD or FRAX score no association remained significant. Both lower FN aBMD and higher FRAX score predicted any incident fracture, MOF and hip fractures with HRs ranging from 1.45–2.56.

Conclusions: This study showed that cortical bone measurements using clinical CT did not add substantial insight into fracture risk beyond FN aBMD and FRAX. We infer from these results that fracture risk related to the deteriorated bone structure seems to be largely captured by a measurement of FN aBMD and the FRAX tool.

1. Introduction

Fracture risk is most frequently assessed using Dual X-ray absorptiometry (DXA) to measure areal bone mineral density (aBMD) and the Fracture Risk Assessment Tool (FRAX), which includes many clinical risk factors [1]. However, these approaches have limitations as the majority of osteoporotic fractures occur in individuals with BMD values above the threshold for osteoporosis and without a high FRAX score [2–4]. Additional bone measurements may enhance the predictive ability of these existing tools.

As 80% of the skeleton is cortical bone, there has been a focus on the association between cortical bone traits and fracture risk during the last two decades [5]. Several cross-sectional and cohort studies have shown associations between both cortical and trabecular bone measurements and fracture risk, using high-resolution peripheral quantitative computed tomography (HR-pQCT) [6–16] and QCT [17–19]. The BoMIC study of 7254 women and men from eight cohorts showed no strong association between cortical porosity and incident fractures, as opposed

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to findings from cross-sectional studies [12,14–16]. The BoMIC study used the threshold based Scanco software for assessment of bone microarchitecture. Only one prospective study has used the StrAx1.0 software, which takes into account the trabecularization of cortical bone when separating cortical from trabecular bone compartment [9,20].

In contrast to HR-pQCT, clinical CT is readily available in most health care institutions worldwide. CT is used for diagnostics and pre-operative planning at departments of orthopedic surgery. If already obtained CT images could be used for fracture prediction instead of DXA, it would be beneficial for both patients and health care institutions concerning costs and efficacy.

HR-pQCT can only be applied at peripheral sites, and it is unclear whether peripheral measurements are representative of bone traits at central sites. For measurements at the fracture location, HR-pQCT is at a disadvantage with respect to the most important osteoporotic fractures, i.e. spine and hip. To the best of our knowledge, no prospective study has used the StrAx1.0 software to assess the bone structure at a central site for prediction of fractures. We examined whether cortical bone structure of the proximal femur in postmenopausal women predicts incident fracture at any location, major osteoporotic fractures (MOF) or hip fractures, independent of FN aBMD and FRAX score.

2. Material and methods

2.1. Subjects

The Tromsø Study is a large single center population-based study in Norway and consists of seven surveys, conducted between 1974 and 2015–2016 [21,22]. Among the 27,158 participants in the fourth survey in 1994–1995 (Tromsø 4), all women with non-vertebral fractures were registered from the x-ray archives of the University Hospital of North Norway between 1994 and 1995 and 2010 (Fig. 1). This fracture registration has been validated as previously reported [23,24]. In a prior nested case-control study initiated in 2011, a total of 1250 women who had suffered a fracture of the hip, wrist or proximal humerus were identified [14].

All the 760 women who were residing in Tromsø were invited. Women who were premenopausal, receiving AOD, had pathological fracture or implanted hip prosthesis or osteosynthesis were excluded, leaving 264 cases attending the study (Fig. 1). Randomly selected age-matched fracture-free controls were invited from the Tromsø 4. After applying the same exclusion criteria, 260 of the 1186 invited controls were included in the final analysis. Further, 15 women were excluded because of ongoing hormone therapy and 66 due to movement artifacts on CT images. Thus, a total of 443 women, 211 cases and 232 controls, were included in the prior nested case-control study. We pooled these 443 postmenopausal women aged 54–94 years at baseline (November

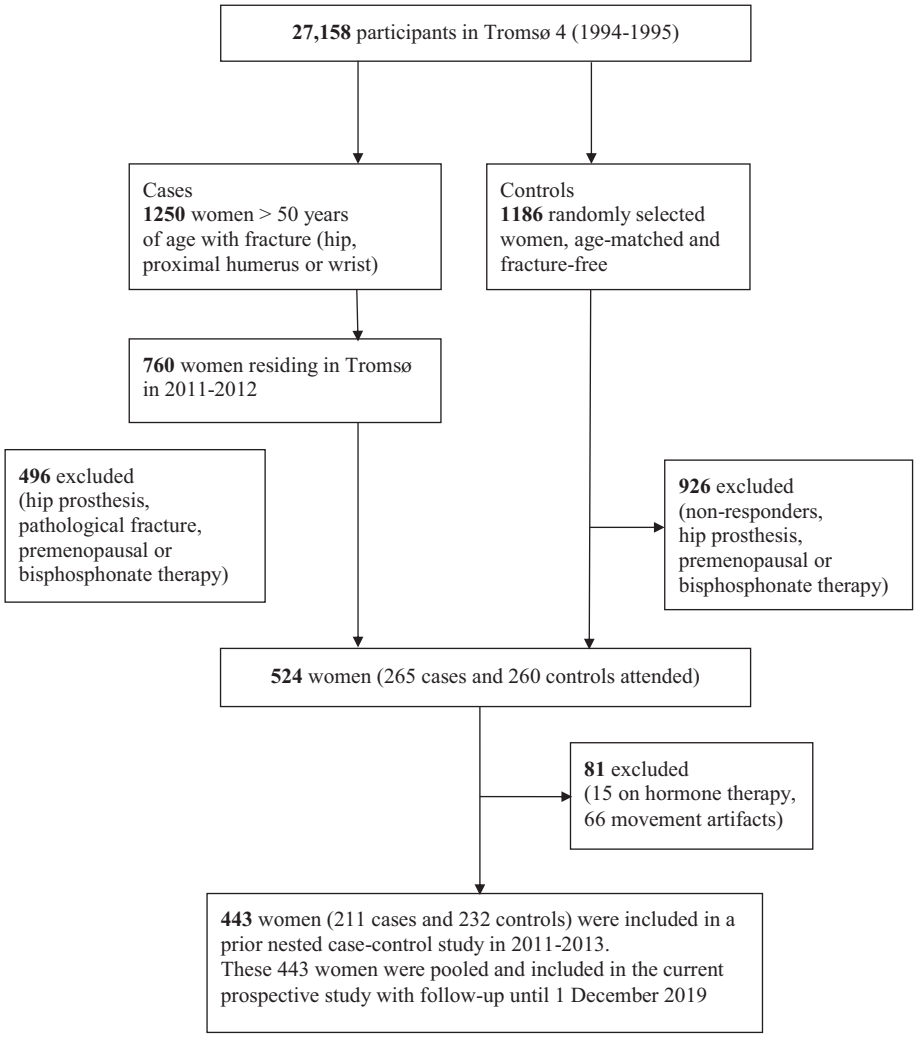

Fig. 1. Participants in the prior nested case-control study in 2011–2013, based on the Tromsø Study, with follow-up until 2019 in the current prospective study.

2011–January 2013) and collected information about their incident fractures during follow-up until 1 December 2019 in this current prospective study. All participants provided written informed consent, and the study was approved by the Regional Committee of Research Ethics (REK reference 2010/2282) and the Norwegian Data Inspectorate.

2.2. Baseline assessments

Baseline information was collected from November 2011 through January 2013 in the prior nested case-control study. Self-administered questionnaires included information concerning the participants' fracture history, diseases, use of medication and lifestyle. Body weight and standing height were measured in light clothing without shoes, and body mass index (BMI) was calculated. Femoral neck (FN) aBMD was measured using DXA (GE Lunar Prodigy, Lunar Corporation, Madison, WI, USA) scans of the nondominant hip. In case of a previous hip fracture, the contralateral side was measured. The coefficient of variation (CV) was 1.7%.

The FRAX score for 10-year probability of MOF was calculated using the FRAX tool, which includes age, sex, weight, height, previous fracture, parental hip fracture, glucocorticoid use, smoking, rheumatoid arthritis, secondary osteoporosis, alcohol consumption and FN aBMD.

Bone structure was assessed at the nondominant hip using CT scans (Siemens Somatom Sensation 16, Erlangen, Germany) with an in-plane resolution of 0.74 mm, and slice thickness of 0.6 mm as previously reported in details [14,25]. The hip was scanned from just proximal to the femoral head to 2 cm distal to the lesser trochanter. Images were transferred to Melbourne, Australia for analysis using the StrAx1.0 software [20]. The region of interest (ROI) was confined to the 3.7 mm subtrochanteric region distal to the lesser trochanter and standardized by starting at the tip of the lesser trochanter, because the cortex is thicker in this region compared to the cortices at the femoral head, femoral neck, and the greater trochanter. Figures of ROI are previously published [25,26]. The thicker cortex at the subtrochanteric site (range 2.3–6 mm) is suitable for studying cortical bone structure. However, due to the limited amount of trabecular bone these analyses were omitted. The StrAx1.0 software is a density-based method that automatically selects attenuation profile curves and segments the bone into its compact-appearing cortex, outer and inner transitional zones (OTZ and ITZ), and trabecular compartment [14,20,25]. This segmentation is performed similarly in any CT image regardless of its resolution. Accuracy of porosity measurements have been validated by comparing HR-pQCT and clinical CT measurements of the same ROI at the subtrochanteric region of the proximal femur in eleven cadaveric specimens [26]. The correlation between porosity measured by HR-pQCT and CT ranged from $r = 0.94$ for total cortical porosity to $r = 0.86$ for the ITZ.

The StrAx1.0 software quantified the femoral subtrochanteric porosity of the total cortex, compact cortex, OTZ and ITZ, cortical area, cortical thickness, and cortical volumetric BMD (vBMD). The total cortical porosity as assessed by StrAx1.0 includes porosity not only of the compact cortex but also the transitional zone, and porosity produced by large pores (>100 μm) and small pores (<100 μm), as StrAx quantifies porosity as a fraction of void regardless of size of the pores [20]. The cortical porosity presented here is the average void volume fraction within the total cortex. The porosity quantified by this algorithm is the proportion of emptiness within each voxel or the fraction of the bone occupied by void (porosity). The size and number of pores were not determined by using this software.

2.3. Follow-up and incident fractures

Follow-up time was defined as the years contributed by each participant from the date of the baseline visit (2011–2013) to the following events: the first incident fracture of any type, to death, when the participants moved, or the closing date (1 December 2019), whichever occurred first. Follow-up time to the first incident MOF and follow-up time to the first incident hip fracture were similarly defined as the years until the first fracture event within each of these fracture groups following the same procedure. Therefore, the number of fractures within each of the fracture groups varied, depending on which type of fracture that occurred first.

Information on all incident fractures was obtained by scrutinizing the participants' medical records and the radiographic reports from the archives of The University Hospital of North Norway in Tromsø. All incident fractures were adjudicated by a physician. Fractures of fingers, toes, skull, and face were not included. Some of the vertebral fractures were incidental findings, and the date of the x-ray scan was registered as the date of fracture.

2.4. Statistical analysis

Normally distributed baseline characteristics are presented as mean ± standard deviation (SD). The FRAX score variable with skewed distribution is presented as median and range and was log-transformed for further statistical analysis. Baseline characteristics of women with any type of incident fractures, MOF or hip fractures were compared with the women without any incident fracture using analysis of variance (ANOVA). The analysis were adjusted for age and/or previous fracture, except for the models of FRAX that were unadjusted.

Associations between baseline bone parameters and incident fracture of any type, MOF or hip fractures were determined using Cox's proportional hazard models. Hazard ratios (HRs) with 95% confidence intervals (CIs) are presented per SD difference in bone parameters in the expected direction of increased fracture risk. The models of bone parameters were analyzed unadjusted, adjusted for age, BMI, and previous fracture, and additionally adjusted for FN aBMD. To further test whether the bone parameters predicted fractures independent of the FRAX score, models were adjusted for FRAX scores only. The final models included all the covariates with $p < 0.05$. Values of $p < 0.05$ were considered significant. The statistical analysis was performed using SAS Software package, v9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

The baseline characteristics of the fracture-cases and the age-matched fracture-free controls from the prior nested case-control study are presented in Table 1 (14). In brief, the fracture-cases had lower FN aBMD (794 vs. 860 mg/cm^2), higher FRAX score (15.1 vs. 10.8%), smaller cortical area (409 vs. 417 mm^2), thinner cortices (4.06 vs. 4.36 mm), and higher total cortical porosity (43.8 vs. 41.7%) compared to the controls.

3.1. Incident fractures

During a median follow-up of 7.2 years (range 0.1–8.0), 114 (25.7%) women had one or more incident fractures, 77 women had a MOF, and 17 women had a hip fracture as the first incident fracture (Table 2). Women in the baseline fracture-group sustained 63% of the incident fractures and women in the control-group sustained 37%. Of the 114 women with incident fractures, 109 sustained 1 fracture, 23 sustained 2 fractures, 4 sustained 3 fractures and 1 sustained 4 fractures. All participants except two had low-energy fractures. Exclusion of these two women did not change the results.

3.2. Women with and without incident fractures

Women with any incident fracture had lower baseline FN aBMD, higher FRAX score, and a higher percentage with previous fractures compared to women without incident fractures (Table 3). There was no difference regarding porosity of the compact cortex, OTZ, ITZ, cortical area or cortical thickness between the groups. Women with incident MOF were older, had lower FN aBMD, higher FRAX score, and a higher

Table 1
Baseline characteristics of postmenopausal women by fracture status in the prior nested-case control study from the Tromsø study, who were pooled for follow-up in this prospective study.

	Cases	Controls	p
n	211	232	
Age (years)	68.4 ± 7.7	68.3 ± 6.7	0.937
Weight (kg)	68.9 ± 10.5	70.0 ± 10.8	0.280
Height (cm)	162.7 ± 6.1	161.2 ± 6.6	0.011
Body mass index (kg/m^2)	26.0 ± 3.8	27.0 ± 4.3	0.015
Physical activity (hours/week)	2.6 ± 1.6	2.5 ± 1.7	0.421
Currently smoking, n (%)	29 ± 13.7	24 ± 10.3	0.257
Alcohol intake (drinks/week)	3.2 ± 3.7	3.3 ± 3.5	0.407
Teetotaler, n (%)	22 (10.4)	18 (7.8)	0.328
History of previous fracture, n (%)	54 ± 25.6	0	
Parental hip fracture, n (%)	34 ± 16.3	37 ± 16.0	0.469
Self-reported good health, n (%)	147 ± 70.3	165 ± 71.1	0.958
Rheumatoid arthritis, n (%)	11 ± 5.2	8 ± 3.5	0.407
Oral corticosteroid use, n (%)	8 ± 3.8	2 ± 0.9	0.023
Take calcium supplements, n (%)	44 ± 20.9	28 ± 12.1	0.007
Take Vitamin D supplements, n (%)	163 ± 77.3	166 ± 71.6	0.278
Femoral neck (FN) aBMD (mg/cm^2)	794 ± 100	860 ± 110	<0.001
FRAX score for MOF (%)	15.1 ± 8.4	10.8 ± 4.9	< 0.001
Femoral subtrochanteric bone structure			
Total cortical porosity (%)	43.8 ± 4.35	41.7 ± 3.39	< 0.001
Compact cortex porosity (%)	35.3 ± 3.10	34.3 ± 2.67	0.001
Outer TZ porosity (%)	45.6 ± 2.41	45.3 ± 2.18	0.216
Inner TZ porosity (%)	84.1 ± 1.57	84.2 ± 1.43	0.570
Cortical area (mm^2)	409 ± 39.1	417 ± 39.4	0.029
Cortical thickness (mm)	4.06 ± 0.58	4.36 ± 0.54	< 0.001
Cortical vBMD (mg HA/cm^3)	1025 ± 72.6	1059 ± 56.6	< 0.001
Total bone vBMD (mg HA/cm^3)	684 ± 113	750 ± 90.0	< 0.001

Numbers are mean ± SD or number (%).
Cases and controls are compared using ANCOVA adjusted for age.
FRAX = Fracture Risk Assessment Tool for calculation of the 10-year probability of a major osteoporotic fracture (MOF), aBMD = areal bone mineral density, vBMD = volumetric BMD, TZ = transitional zone.

Table 2
Number of women with any type of incident fracture, major osteoporotic fracture (MOF) and hip fracture as the first fracture that occurred during follow-up from 2011 to 2013 to 2019.

	Any fracture	MOF	Hip
Vertebral	15	17	
Hip	13	14	17
Proximal humerus	11	11	
Wrist	33	35	
Clavicle	4		
Rib	3		
Pelvis	1		
Elbow	5		
Hand	8		
Patella	2		
Ankle	10		
Foot	9		
Total number	114	77	

The number of each type of fracture within the fracture groups varied because we included the first fracture of any type in the analysis of any fracture, the first MOF in the analysis of MOF and the first hip fracture in the analysis of hip fracture that occurred during follow-up.

percentage with previous fractures compared to women without incident fractures. There was no difference regarding porosity of the compact cortex, OTZ, ITZ, cortical area or cortical thickness between the groups. Women with incident hip fractures were older, had higher FRAX score, higher total cortical porosity and lower cortical vBMD compared to women without incident fractures. As porosity of the cortical compartments did not differ between women with and without fractures, only total cortical porosity was included in further analyses of fracture prediction for simplicity.

3.3. Cortical measurements and any incident fracture, MOF and hip fractures

Cortical bone structure did not predict any incident fracture or MOF (Tables 4 and 5). Per SD higher cortical porosity, thinner cortices, and lower cortical vBMD, HRs (95% CI) for incident hip fractures were 1.46 (1.01–2.11), 1.62 (1.02–2.57), 1.46 (1.01–2.11) as shown in Table 6. All above-mentioned analyses were adjusted for age, BMI, and previous fracture. None of the associations remained significant after additionally adjustment for FN aBMD or FRAX. Both lower FN aBMD and higher FRAX score predicted any incident fracture, MOF and hip fractures with HRs ranging from 1.45–2.56. The correlations between cortical porosity, area, and thickness and FN aBMD were − 0.37, 0.52, 0.47, all $p < 0.001$.

3.4. Osteopenia, cortical porosity and any incident fractures, MOF and hip fractures

In 255 women with osteopenia (T-score between −2.5 and − 1.0), 79 women had incident fractures of any type, 53 had MOF and 13 had hip fractures. Cortical porosity did not predict any type of fracture (HR 1.05; 0.85–1.31) or MOF (HR 1.10; 0.86–1.42). Cortical porosity predicted hip fractures independent of FN aBMD and age (HR 1.55; 1.00–2.39) $p = 0.049$, but not independent of FRAX (HR 1.55; 0.97–2.47) $p = 0.068$.

4. Discussion

This is the first prospective study of the associations between cortical bone parameters and incident fractures using QCT images obtained at the hip and analyzed using the StrAx1.0 software. Each SD higher cortical porosity, thinner cortices, and lower cortical vBMD predicted hip fracture with increased risk of 46–62%. Each SD lower FN aBMD and higher FRAX score increased the risk for any incident fracture, MOF and hip fractures with HRs between 1.45 and 2.56.

Several cross-sectional studies have shown associations between cortical bone structure and risk of fracture using HR-pQCT [8,12,14–16] and QCT [17–19]. In a prospective study of 456 older Swedish men, cortical area and cortical thickness of the distal tibia predicted any incident fracture and MOF independently of aBMD, but cortical porosity did not [13]. In other studies using HR-pQCT, cortical area of the distal tibia and/or distal radius predicted incident fractures, whereas cortical thickness showed ambiguous results [6,7,9–11,27]. Cortical thickness, cortical and trabecular vBMD assessed using QCT of the hip were associated with hip fracture in some small case control studies [17,19]. None of the prospective studies based on HR-pQCT and QCT [28,29] reported an association between cortical bone structure and incident fracture independent of FN aBMD, except for Biver et al., the only study using both Scanco and StrAx1.0 software [9].

Most of the prospective studies, also the large BoMIC study, used the Scanco software. Scanco is a threshold-based method for separation of cortex from trabecular bone, and quantifies porosity by including only pores above 100 μm and empty voxels, resulting in an underestimation of porosity [5,25]. In contrast, the StrAx1.0 software is a density-based method that takes into account the transitional zone and the partial volume effect when quantifying porosity within each compartment [20]. The total cortical porosity assessed by StrAx1.0 is the average porosity of the compact cortex, OTZ and ITZ and it is therefore higher. Cortical porosity at the distal radius has been shown to differ within a range of 1–13% by Scanco and 38–77% by StrAx1.0 software [9]. It has been reported that the threshold-based method underestimates porosity by 3–11% and that a density-based method overestimates porosity by 6–21% [30], however, this is not reported for StrAx1.0. The threshold-based method could not quantify the volume of the pores below 100 μm, only larger pores, whereas the density-based StrAx1.0 method could not quantify the size and number of the pores. Capturing the correct cut-off between the gradual change in attenuation from cortical to trabecular bone is challenging, because trabecularized cortical bone of the

Table 3
Baseline characteristics of women without any incident fracture, and women with any incident fracture, MOF and hip fracture.

	Without any incident fracture ($n = 329$)	Any fracture ($n = 114$)	p	MOF ($n = 77$)	p	Hip fracture ($n = 17$)	p
Age (years)	68.0 ± 7.0	69.4 ± 7.8	0.112[a]	69.9 ± 8.1	0.031[a]	75.8 ± 7.8	<0.001[a]
Body mass index (kg/m^2)	26.7 ± 4.3	25.9 ± 3.4	0.092	25.6 ± 3.5	0.062	26.7 ± 3.4	0.720
FN aBMD (mg/cm^2)	842 ± 110	792 ± 105	0.004	783 ± 99	0.007	765 ± 96	0.117
FRAX score (%)	10 (4–44)	15 (5–48)	<0.001	15 (5–48)	<0.001	20 (7–32)	<0.001
Previous fracture, n (%)	139 (42.3)	72 (63.2)	<0.001[b]	53 (68.8)	<0.001[b]	11 (64.7)	0.063[b]
Femoral subtrochanteric bone structure							
Total cortical porosity (%)	42.5 ± 3.94	43.4 ± 4.13	0.271	44.0 ± 4.34	0.092	45.3 ± 5.82	0.035
Compact cortex porosity (%)	34.7 ± 2.87	35.0 ± 3.05	0.616	35.4 ± 3.14	0.223	35.7 ± 3.65	0.286
Outer TZ porosity (%)	45.4 ± 2.25	45.6 ± 2.43	0.423	45.8 ± 2.53	0.191	46.0 ± 2.60	0.339
Inner TZ porosity (%)	84.0 ± 1.53	84.3 ± 1.37	0.050	84.4 ± 1.44	0.054	84.4 ± 1.82	0.443
Cortical area (mm^2)	415 ± 41.0	410 ± 34.7	0.535	407 ± 33.8	0.366	398 ± 31.0	0.198
Cortical thickness (mm)	4.23 ± 0.58	4.16 ± 0.56	0.883	4.08 ± 0.59	0.539	3.83 ± 0.77	0.071
Cortical vBMD (mg/cm^3)	1047 ± 65.8	1031 ± 68.9	0.270	1000 ± 97.2	0.092	1000 ± 97.2	0.035

Values are mean ± standard deviation, median (range) or number (%).
FN = femoral neck, aBMD = areal bone mineral density, FRAX = Fracture Risk Assessment Tool for calculation of 10-year probability of major osteoporotic fracture (MOF), vBMD = volumetric BMD, TZ = transitional zone.
All fracture groups were compared with women without any incident fracture using analysis of variance.
All the models were adjusted for age and previous fracture, except:
[a] Adjusted for previous fracture.
[b] Adjusted for age, the models of FRAX were unadjusted.

Table 4
Hazard ratio (95% CI) for any incident fracture per SD difference in baseline measurements.

	SD unit	Unadjusted	Adjusted[a]	Additionally adjusted for FN aBMD	Adjusted for FRAX score only
Age	+7.2	1.18 (0.98–1.41)			
Body mass index (BMI)	−4.1 kg/m^2	1.18 (0.98–1.42)			
Previous fracture	Yes vs no	1.88 (1.28–2.76)[b]			
FN aBMD	−110 mg/cm^2	1.52 (1.24–1.87)[c]	1.36 (1.08–1.71)[b]		
Log-FRAX score	+1.00	1.49 (1.24–1.78)[c]			
Femoral subtrochanteric bone structure					
Total cortical porosity	+4.01%	1.17 (0.99–1.39)	1.06 (0.89–1.26)	1.00 (0.83–1.19)	1.07 (0.90–1.27)
Cortical area	-39.5 mm^2	1.12 (0.93–1.34)	1.03 (0.85–1.26)	0.88 (0.71–1.11)	1.01 (0.83–1.22)
Cortical thickness	-0.58 mm	1.07 (0.89–1.29)	0.93 (0.76–1.13)	0.83 (0.67–1.02)	0.94 (0.78–1.14)
Cortical vBMD	−66.9 mg/cm^3	1.17 (0.99–1.39)	1.06 (0.89–1.26)	1.00 (0.83–1.19)	1.07 (0.90–1.27)

FN = femoral neck, aBMD = areal bone mineral density, FRAX = Fracture Risk Assessment Tool for calculation of 10-year probability of major osteoporotic fracture, vBMD = volumetric BMD.
[a] Adjusted for age, BMI and previous fracture.
[b] $p < 0.01$.
[c] $p < 0.001$.

Table 5
Hazard ratio (95% CI) for incident major osteoporotic fractures (MOF) per SD difference in baseline measurements.

	SD unit	Unadjusted	Adjusted[a]	Additionally adjusted for FN aBMD	Adjusted for FRAX score only
Age	+7.2	1.26 (1.01–1.58)[b]			
Body mass index (BMI)	−4.1 kg/m^2	1.28 (1.01–1.62)[b]			
Previous fracture	Yes vs no	2.31 (1.42–3.77)[d]			
FN aBMD	−110 mg/cm^2	1.65 (1.28–2.13)[d]	1.38 (1.04–1.83)[c]		
Log-FRAX score	+1.00	1.45 (1.16–1.81)[c]			
Femoral subtrochanteric bone structure					
Total cortical porosity	+ 4.01%	1.31 (1.07–1.60)[c]	1.15 (0.94–1.40)	1.08 (0.88–1.34)	1.21 (0.99–1.48)
Cortical area	- 39.5 mm^2	1.21 (0.97–1.52)	1.09 (0.86–1.39)	0.94 (0.71–1.24)	1.11 (0.88–1.41)
Cortical thickness	- 0.58 mm	1.22 (0.98–1.53)	1.02 (0.80–1.29)	0.89 (0.68–1.16)	1.10 (0.87–1.38)
Cortical vBMD	−66.9 mg/cm^3	1.31 (1.07–1.60)[c]	1.15 (0.94–1.40)	1.08 (0.88–1.34)	1.21 (0.99–1.48)

FN = femoral neck, aBMD = areal bone mineral density, FRAX = Fracture Risk Assessment Tool for calculation of 10-year probability of major osteoporotic fracture, vBMD = volumetric BMD.
[a] Adjusted for age, BMI and previous fracture.
[b] $p < 0.05$.
[c] $p < 0.01$.
[d] $p < 0.001$.

inner cortex may look similar to trabecular bone [31]. The pathophysiology of bone can be seen as a lower bone mass or as a larger volume of pores. The latter is intuitive as a bone full of pores are weaker and more likely to fracture.

In the only prior prospective study using StrAx1.0, cortical porosity of the ITZ of the distal tibia and distal radius predicted incident fractures independent of FN aBMD but not independent of distal radius aBMD [9]. The reason for this could be that the intracortical remodeling is more

Table 6
Hazard ratio (95% CI) for incident hip fractures per SD difference in baseline measurements.

	SD unit	Unadjusted	Adjusted[a]	Additionally adjusted for FN aBMD	Adjusted for FRAX score only
Age	+7.2	2.73 (1.77–4.22)[b]			
Body mass index (BMI)	−4.1 kg/m^2	0.96 (0.60–1.52)			
Previous fracture	Yes vs no	1.94 (0.72–5.24)			
FN aBMD	−110 mg/cm^2	2.01 (1.15–3.54)[b]	1.55 (0.88–2.75)		
Log-FRAX score	+1.00	2.56 (1.60–4.11)[d]			
Femoral subtrochanteric bone structure					
Total cortical porosity	+4.01%	1.69 (1.13–2.52)[b]	1.46 (1.01–2.11)[b]	1.36 (0.90–2.06)	1.33 (0.88–2.01)
Cortical area	-39.5 mm^2	1.52 (0.93–2.53)	1.54 (0.91–2.59)	1.32 (0.71–2.45)	1.26 (0.74–2.13)
Cortical thickness	-0.58 mm	1.92 (1.21–3.05)[c]	1.62 (1.02–2.57)[b]	1.51 (0.88–2.59)	1.48 (0.92–2.39)
Cortical vBMD	−66.9 mg/cm^3	1.69 (1.13–2.52)[b]	1.46 (1.01–2.11)[b]	1.36 (0.90–2.06)	1.33 (0.88–2.01)

FN = femoral neck, aBMD = areal bone mineral density, FRAX = Fracture Risk Assessment Tool for calculation of 10-year probability of major osteoporotic fracture, vBMD = volumetric BMD.
[a] Adjusted for age, BMI and previous fracture.
[b] $p < 0.05$.
[c] $p < 0.01$.
[d] $p < 0.001$.

pronounced in the cortex adjacent to the marrow cavity, which corresponds to the ITZ [5]. However, the association between ITZ and incident fractures is unclear as most studies have used the Scanco software which does not enable measurement of this compartment. Although the present study had similar sample size and number of incident fractures in postmenopausal women of same age as Biver et al., we did not find an association between cortical porosity and incident fractures independent of FN aBMD [9]. Measurements of the cortical bone structure at the distal radius may better predict MOF, which is dominated by forearm fracture. The discrepancy in the results may be due to different sites of measuring bone structure. The finding of increased risk for hip fracture in postmenopausal women with thinner cortices and higher total cortical porosity of the femoral subtrochanteric site is in agreement with the findings by Sundh et al. who reported increased risk of hip fractures in older women with thinner cortices and higher cortical porosity at the distal tibia in a case-control study [12].

A strength of this study is its prospective design with a median follow up 7.2 years, including x-ray verified fractures in subjects from a general population and a validated fracture registry. The subjects were postmenopausal women who are at high-risk for fragility fractures. Moreover, images were obtained at the hip, a central site, which is the site of the most serious fragility fracture. The study has several limitations. First, the moderate sample size could result in a lack of statistical power, particularly for the analysis of incident hip fractures. The non-significant HR for FN aBMD to predict hip fractures (Table 6) may also reflect insufficient statistical power of this subgroup analysis and indicates that our results related to hip fractures have to be interpreted cautiously. A second limitation is the potential healthy selection bias, as women who were older and less healthy were unable to attend. Third, the contribution of trabecular bone traits to fracture risk could not be assessed because of the very small proportion of trabecular bone in the femoral subtrochanteric region. Preferably measurements at the femoral neck should have been included in the current study, as this is one of the most important fracture locations. Existing hip CT scans covering the complete hip may be used for opportunistic screening.

In conclusion, some cortical bone parameters were associated with incident fractures, before but not after adjustment for FN aBMD or FRAX in postmenopausal women in this Norwegian population-based cohort. This study showed that cortical bone measurements using clinical CT did not add substantial insight into fracture risk beyond FN aBMD and FRAX. We infer from these results that fracture risk related to the deteriorated bone structure seems to be largely captured by a measurement of FN aBMD and the FRAX tool.

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CRediT authorship contribution statement

Frida Igland Nissen: Conceptualization, Investigation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Camilla Andreasen:** Conceptualization, Investigation, Writing – review & editing. **Tove Tveitan Borgen:** Writing – review & editing. **Åshild Bjørnerem:** Conceptualization, Investigation, Resources, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition. **Ann Kristin Hansen:** Formal analysis, Data curation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

TTB has received speaker fees from Amgen and UCB.
The other authors have nothing to declare.

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