Paper II

Women with Fracture, Unidentified by FRAX, but Identified by Cortical Porosity, have a Different Patient Profile that Contribute to Fracture Risk

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Disclosures

The authors have nothing to disclose.

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 FRAX, but identified by cortical porosity, have a different patient profile that contributes to their fracture risk. 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 StrAx1.0 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), larger total and medullary cross-sectional areas (669 vs. 593 and 245 vs. 190 mm^2), higher cross-sectional moment of inertia (2619 vs. 2388 cm^4) and lower cortical and total volumetric BMD (942 vs. 1053 and 586 vs. 699 mg HA/cm^3), all $p < 0.001$. 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 a patient profile that captures additional fracture risk components, not captured by FRAX.

Key words: bone size, cortical porosity, fracture, FRAX, postmenopausal women

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 (BMD) 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). Many bone features contribute to bone strength, such as the bone architecture and geometry (6, 7). A larger size is important for bone strength, 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 Strax1.0 software, cortical porosity of the inner transitional zone at 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 patient profiles of the additional individuals with fractures who are identified by cortical porosity independently of FRAX. We wanted to test the hypothesis that women with fracture, who are unidentified by FRAX, but identified by cortical porosity, have a different patient profile that contributes to their fracture risk.

Materials and methods

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 controls and 211 fracture cases (4 hip, 181 wrist, and 26 proximal humerus). The median time since their 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. 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.

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 StrAx1.0 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 as shown in Fig. 1 (15, 27).

The StrAx1.0 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 StrAx1.0 software (15). The porosity quantified by this algorithm is the proportion of emptiness within each voxel or the fraction of the bone that is void, with CV of 0.3-2.3% (15). StrAx1.0 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 StrAx1.0 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).

Statistical analyses

We present mean and standard error of the mean (SE) in four groups. Group 1: 35 fracture cases identified by high FRAX score (threshold >20%), but unidentified by high cortical porosity (threshold >80th percentile). Group 2: 43 fracture cases unidentified by high FRAX score, but identified by high cortical porosity. Group 3: 115 fracture cases unidentified by both high FRAX score and cortical porosity. Group 4: 232 age-matched fracture-free controls. The characteristics the women within each of the groups were compared using age-adjusted analysis of variance, and the bone parameters were compared after additionally adjustment for height and weight. We used SAS Software, v9.4 (SAS Institute Inc., Cary, NC, USA) and $p < 0.05$ was considered significant.

Results

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 cortical porosity with cut-off >80th percentile identified 61 women, with a sensitivity of 28.9% and specificity of 87.9% (Fig. 2). Of 211 fracture cases, 35 (16.6%) (Group 1) were identified only by high FRAX score, and 43 (20.4%) (Group 2) 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 3) fracture cases were unidentified by either.

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 (all $p < 0.05$, Table 1 and Fig. 3). Otherwise, the FRAX score and the risk factors included in FRAX differed little between Group 2, 3 and 4, except for the higher FN aBMD in controls (Group 4) than in all other groups, $p < 0.001$.

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 porosity of the total cortex (48.7 vs. 42.1%), 14.5% higher porosity of the compact cortex (38.7 vs. 33.8%) and 6.7% higher porosity of the OTZ (47.5 vs. 44.5%), all $p < 0.001$, but not higher porosity of the ITZ (83.9 vs. 84.3%) than those identified by high FRAX score alone (Table 1, Fig. 4). They had 9.0% thinner cortices (3.75 vs. 4.12 mm), 28.9% larger medullary cross-sectional area (CSA) (245 vs.190 mm^2), 12.8% larger total CSA (669 vs. 593 mm^2), and 9.7% higher cross-sectional moment of inertia (CSMI) (2619 vs. 2388 cm^4), 10.5% lower cortical volumetric BMD (vBMD) (942 vs. 1053 mg HA/cm^3), and 16.2% lower total vBMD (586 vs. 699 mg HA/cm^3), all $p < 0.001$. Otherwise, bone traits differed little between Group 1, 3 and 4.

Discussion

We report that fracture cases unidentified by FRAX but identified by cortical porosity, had a different patient profile than the fracture cases identified by FRAX. Those who were 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 relatively larger bone size, larger medullary cavity, thinner and more porous cortices at the femoral subtrochanteric site, than fracture cases identified by FRAX alone. From these results we infer that a

measurement of cortical porosity capture additional fracture risk components, that is not captured by FRAX.

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).

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, 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 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 identified by FRAX.

Women with fracture identified by high cortical porosity, had higher porosity in both the compact-appearing cortex and the outer transitional zone compared to the other three groups. The increased porosity in the outer part of the cortex may cause a greater loss of strengths as it is located more distant to the neutral axis, given the high stress on the outer part of the cortex 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 strength (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 (42-44). Moreover, microcracks located near intracortical pores compromise fracture resistance (45).

Different genetic variants associated with cortical and trabecular bone traits are identified (46), 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 established during growth early in life, which may contribute to fracture risk in younger age (35). In addition, the fracture cases who unidentified by either high FRAX or cortical porosity, 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.

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 were 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 StrAx1.0 software is vulnerable to motion artifact.

In conclusion, fracture cases identified by high cortical porosity alone had a different patient profile compared to those identified by the FRAX alone. 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 patient profile 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. A measurement of cortical porosity may be a marker of a patient profile, 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.

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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 the DXA scanning. Staff at the 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.

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Figure legends

Fig. 1. Cross-section image of proximal femur and its compartments. Segmented computed tomography image obtained at the proximal femur using StrAx1.0, a non-threshold-based segmentation algorithm, showing the total cortex (the area used for the cortical porosity measurements), consisting of the three cortical compartments: compact-appearing cortex, outer and inner (red) transitional zones, and trabecular bone area. Porosity was assessed from QCT slices distal to the lesser trochanter. Reproduced with permission from John Wiley and Sons, Zebaze et al. J Bone Miner Res. 31 (2016) 1827–1834 (27).

Fig. 2. Fractures cases identified by high cortical porosity alone, high Fracture Risk Assessment Tool (FRAX) score alone, the overlap, and cases who were unidentified by any measurements.

Fig. 3. Fracture Risk Assessment Tool (FRAX) score, age, femoral neck areal bone mineral density (FN aBMD) and proportion with a prior fracture in these four groups. Group 1: fracture cases identified by FRAX score >20% but unidentified by cortical porosity >80th percentile. Group 2: fracture cases unidentified by high FRAX score, but identified by high cortical porosity. Group 3: fracture cases unidentified by either. Group 4: controls.

Fig. 4. Cortical porosity, cortical thickness, total and medullary cross-sectional area (CSA) and Cross-sectional Moment of Inertia (CSMI) at the femoral subtrochanteric site in four groups. Group 1: fracture cases identified by FRAX score >20% but unidentified by cortical porosity >80th percentile. Group 2: fracture cases unidentified by high FRAX score, but identified by high cortical porosity. Group 3: fracture cases unidentified by either. Group 4: controls.

Table 1. Characteristics of the additional fractures cases identified by high FRAX score alone, those identified by high cortical porosity alone, cases who were unidentified by either, and the controls

	Group 1 Cases with FRAX score >20%	**Group 2 Cases with Porosity >80th percentile**	**Group 3 Cases, not identified by any method**	**Group 4 Fracture free Controls**
n	35	43	115	232
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
FRAX score (%)	**26.2 (1.2)[c,f,i]**	12.3 (0.6)	11.2 (0.3)	10.8 (0.3)
Age (years)	**71.7 (1.3)[a,f,h]**	67.6 (1.1)	66.6 (0.7)	68.3 (0.4)
Height (cm)	162.3 (1.2)[g]	164.1 (0.8)[h]	162.8 (0.6)	161.2 (0.4)
Weight (kg)	69.7 (1.3)	70.3 (1.8)	69.3 (1.0)	70.0 (0.7)
Body mass index (BMI) (kg(m²)	26.6 (0.6)	26.1 (0.7)	26.1 (0.4)	27.0 (0.3)
Physical activity (hours/week)	2.2 (0.3)	2.8 (0.3)	2.7 (0.2)	2.5 (0.1)
Femoral neck aBMD (mg/cm²)	**738 (11.9)[b,f,i]**	806 (12.7)[i]	825 (9.1)[i]	860 (7.3)
History of previous fracture, n (%)	**22 (62.9)[c,f]**	10 (23.3)	18 (15.7)	0
Parental hip fracture history, n (%)	**16 (45.7)[c,f,i]**	4 (9.3)	12 (10.4)	37 (16.0)
Currently smoking, n (%)	6 (17.1)	7 (16.3)	14 (12.2)	24 (10.3)
Rheumatoid arthritis, n (%)	**5 (14.3)[e,h]**	2 (4.7)	3 (2.6)	8 (3.4)
Oral corticosteroid use, n (%)	**6 (17.1)[c,f,i]**	1 (2.3)	1 (0.9)	2 (0.9)
Diabetes mellitus type 2, n (%)	3 (8.6)	2 (4.7)	4 (3.5)	13 (5.6)
Self-reported good health, n (%)	20 (58.8)	34 (79.1)	79 (69.3)	165 (71.1)
Take calcium supplements, n (%)	8 (22.9)	11 (25.6)[d]	22 (19.1)	28 (12.1)
Take supplements Vitamin D n, (%)	30 (85.7)	32 (74.4)	86 (74.8)	166 (71.6)
Femoral subtrochanteric parameters				
Porosity total cortex (%)	42.1 (0.4)[c]	**48.7 (0.4)[f,i]**	41.4 (0.2)	41.7 (0.2)
Porosity compact cortex (%)	33.8 (0.3)[c]	**38.7 (0.3)[f,i]**	33.8 (0.2)	34.3 (0.2)
Porosity outer transitional zone (%)	44.5 (0.4)[c,g]	**47.5 (0.3)[f,i]**	44.8 (0.2)[g]	45.3 (0.1)
Porosity inner transitional zone (%)	84.3 (0.2)	83.9 (0.3)	84.0 (0.1)	84.2 (0.1)
Cortical thickness (mm)	4.12 (0.08)[c,g]	**3.75 (0.09)[f,i]**	4.27 (0.04)	4.36 (0.04)
Cortical vBMD (mg HA/cm³)	1053 (6.7)[c]	**942 (6.6)[f,i]**	1065 (3.8)	1059 (3.7)
Cortical CSA (mm²)	403 (6.4)[b,i]	424 (5.8)	410 (3.7)[g]	417 (2.6)
Cortical CSA/Total CSA	0.68 (0.01)[c,d,h]	**0.64 (0.01)[f,i]**	0.71 (0.005)	0.72 (0.003)
Trabecular BV/TV (%)	0.24 (0.03)	0.36 (0.04)[d]	0.24 (0.02)	0.27 (0.02)
Medullary CSA (mm²)	190 (7.2)[c,g]	**245 (10.5)[f,i]**	169 (4.3)	164 (2.8)
Total bone vBMD (mg HA/cm³)	699 (12.5)[c,d,g]	**586 (12.6)[f,i]**	743 (7.9)	750 (5.9)
Total bone CSA (mm²)	593 (10.0)[c]	**669 (12.2)[f,i]**	578 (5.9)	582 (4.0)
Cross-sectional Moment of Inertia	2388 (56)[c]	**2619 (56)[f,i]**	2332 (31)	2361 (21)

Values are mean (SE) or number (%). SE = standard error of the mean.

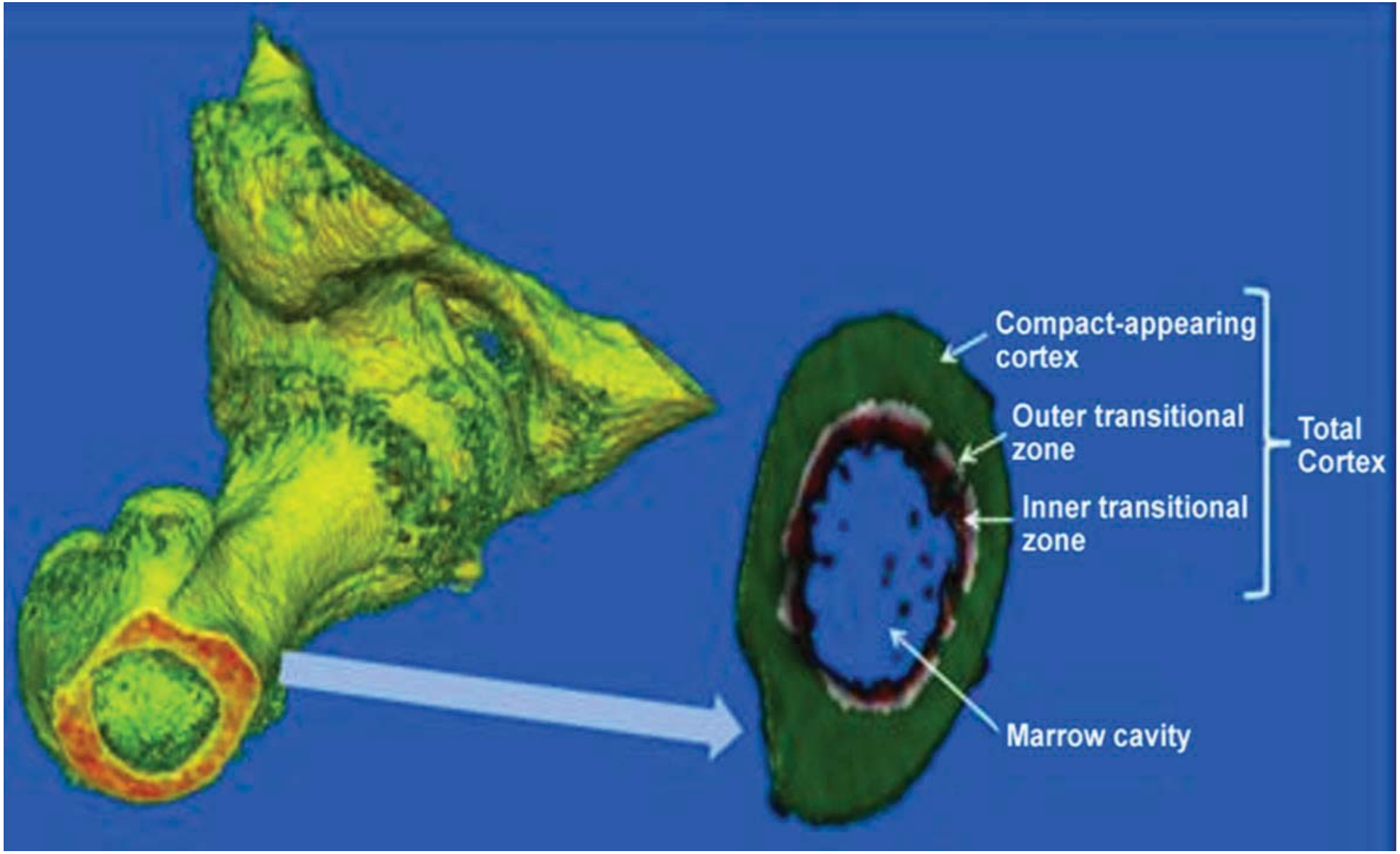
FRAX = Fracture Risk Assessment Tool for calculation of the 10-year probability of a major osteoporotic fracture; aBMD = areal bone mineral density; vBMD = volumetric bone mineral density; HA = hydroxyapatite; CSA = cross sectional area; BV/TV = bone volume per tissue volume.

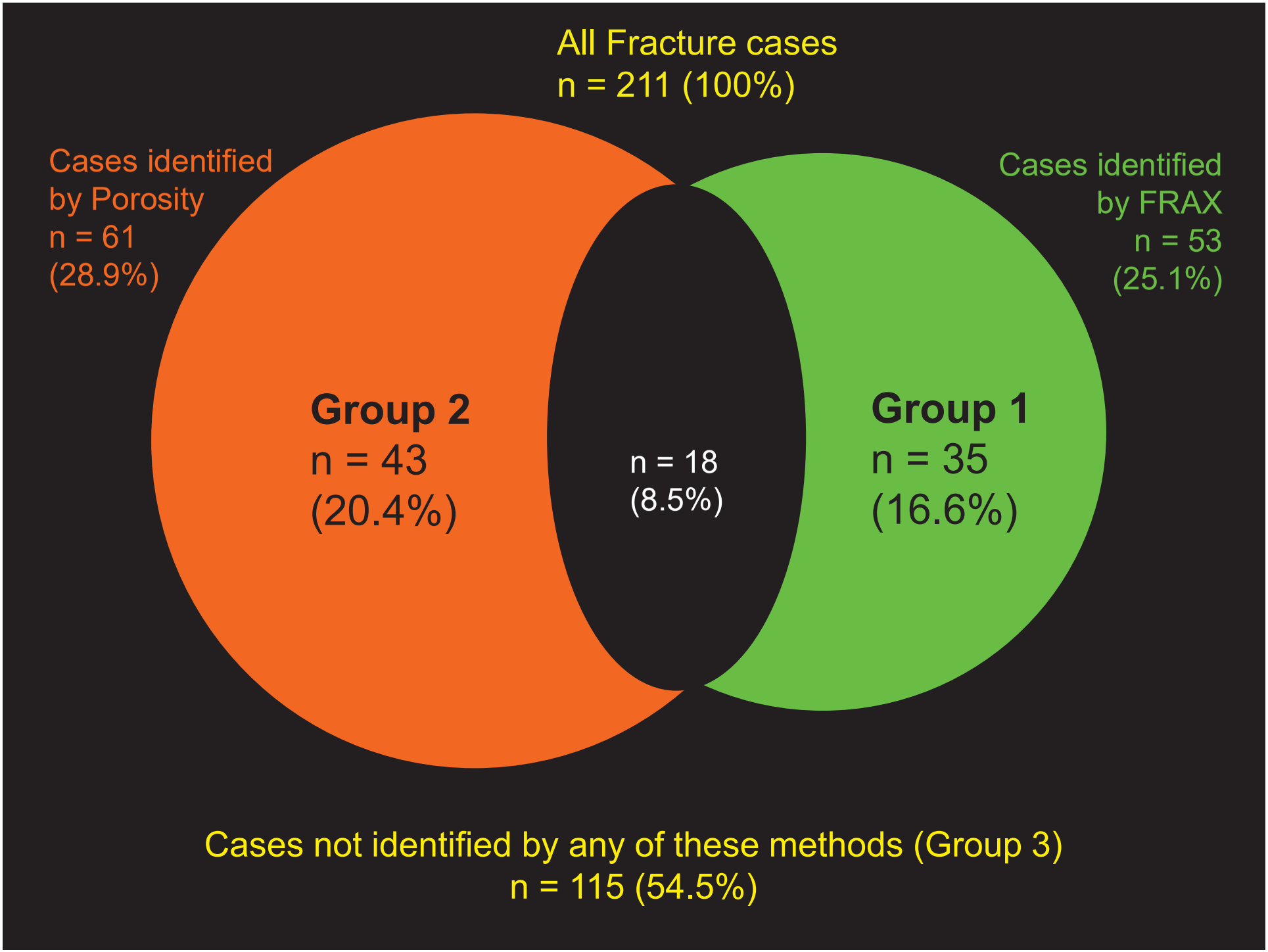
Analysis of variance was used for comparisons of the groups, all comparisons were adjusted for age, and comparisons of bone parameters were additionally adjusted for height and weight.

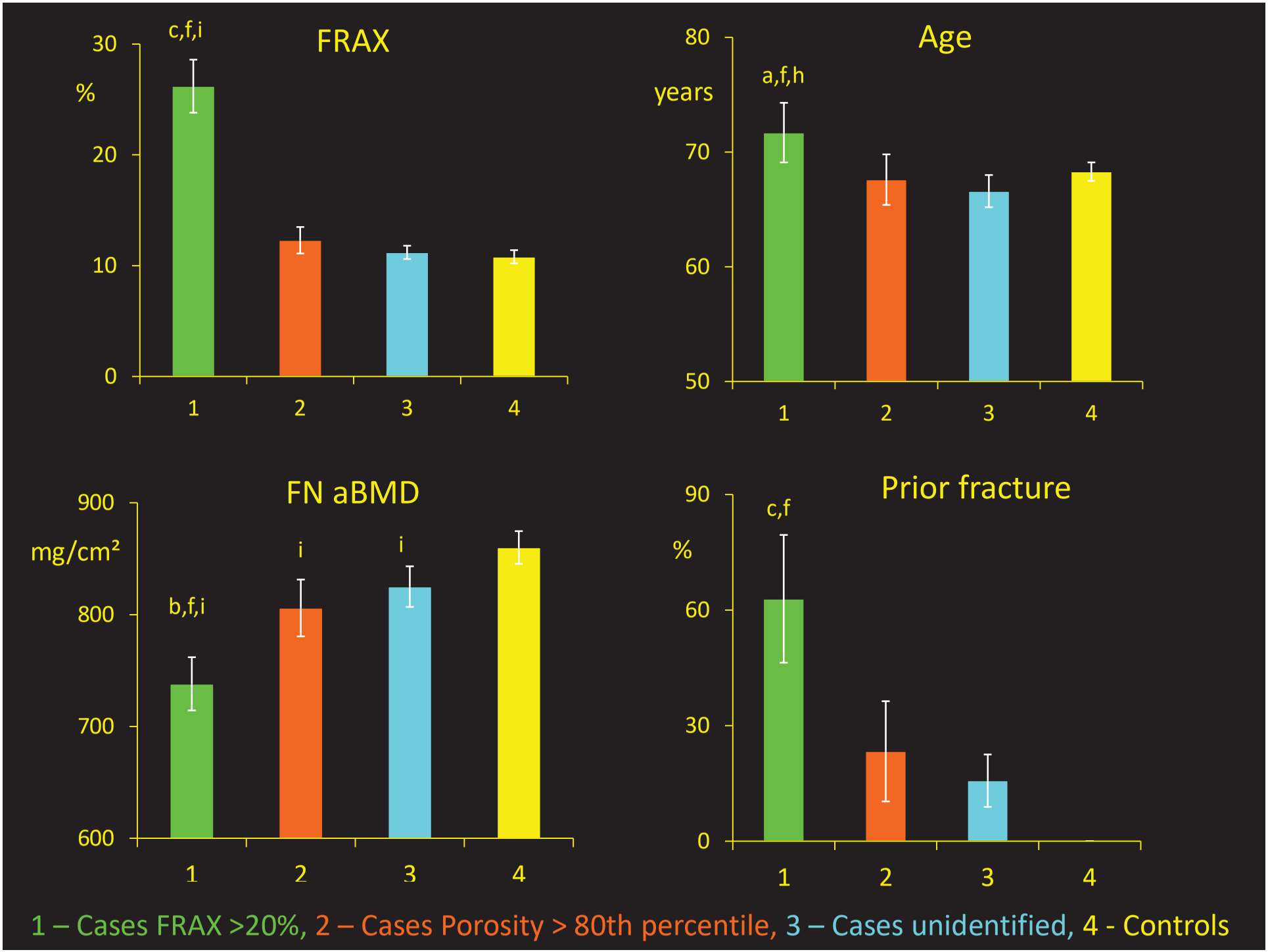
[a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.001$ compared to group 2,

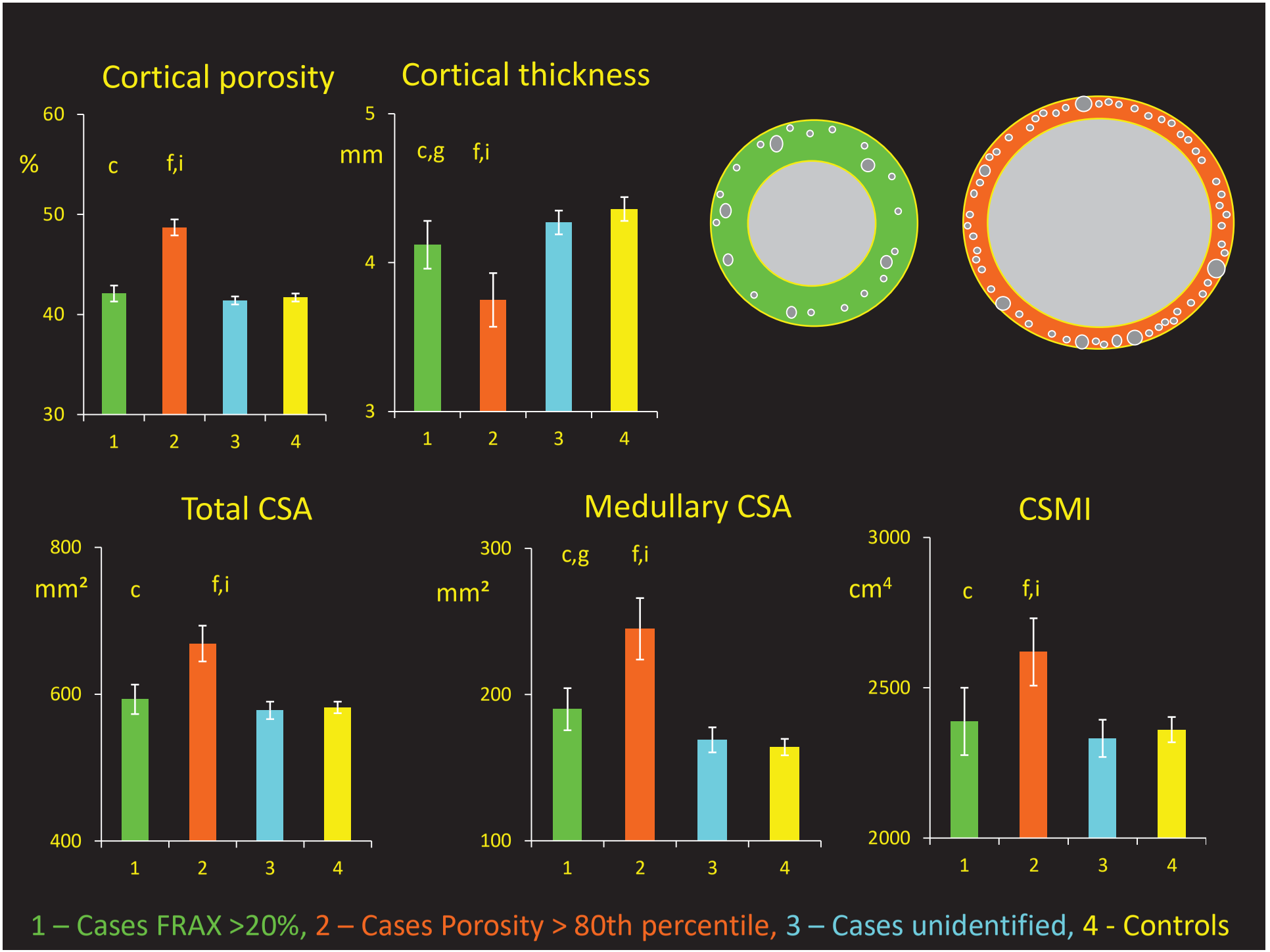
[d]$p < 0.05$, [e]$p < 0.01$, [f]$p < 0.001$ compared to group 3,

[g]$p < 0.05$, [h]$p < 0.01$, [i]$p < 0.001$ compared to group 4.


Compact-appearing cortex
Outer transitional zone
Inner transitional zone
Total Cortex
Marrow cavity


All Fracture cases
n = 211 (100%)
Cases identified by Porosity
n = 61
(28.9%)
Cases identified by FRAX
n = 53
(25.1%)
Group 2
n = 43
(20.4%)
n = 18
(8.5%)
Group 1
n = 35
(16.6%)
Cases not identified by any of these methods (Group 3)
n = 115 (54.5%)


FRAX
%
30
20
10
0
c,f,i
1
2
3
4
Age
years
80
70
60
50
a,f,h
1
2
3
4
FN aBMD
mg/cm²
900
800
700
600
b,f,i
i
i
1
2
3
4
Prior fracture
%
90
60
30
0
c,f
1
2
3
4
1 – Cases FRAX >20%, 2 – Cases Porosity > 80th percentile, 3 – Cases unidentified, 4 - Controls


Cortical porosity
60
%
50
40
30
c
f,i
1
2
3
4
Cortical thickness
5
mm
4
3
c,g
f,i
1
2
3
4
Total CSA
800
mm²
600
400
c
f,i
1
2
3
4
Medullary CSA
300
mm²
200
100
c,g
f,i
1
2
3
4
CSMI
3000
cm⁴
2500
2000
c
f,i
1
2
3
4
1 – Cases FRAX >20%, 2 – Cases Porosity > 80th percentile, 3 – Cases unidentified, 4 - Controls

Appendix A

Questionnaire Pre-screening, Norwegian version