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## Discriminating value of HR-pQCT for fractures in women with similar FRAX scores: A substudy of the FRISBEE cohort

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1 **Discriminating value of HR-pQCT for fractures in women with similar FRAX scores: a**  
2 **substudy of the FRISBEE cohort**

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27 Highlights

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- 28 • 417 women of the FRISBEE cohort, matched for FRAX, were evaluated by HR-pQCT
- 29 • Some HR-pQCT parameters, mainly at radius, are discriminating for prevalent fractures
- 30 • HR-pQCT provides valuable information

## 31 Abstract

32 Areal bone mineral density (aBMD) has a low sensitivity to identify women at high fracture risk. The FRAX  
33 algorithm, by combining several clinical risk factors, might improve fracture prediction compared to aBMD  
34 alone. Several micro-architectural and biomechanical parameters which can be measured by high-resolution  
35 peripheral quantitative computed tomography (HR-pQCT) are associated with fracture risk. [HR-pQCT in  
36 combination or not with finite element analysis \(FEA\) may be used to improve bone strength prediction.](#)

37 Our aim was to assess whether HR-pQCT measurements (densities, cortical and trabecular microarchitecture,  
38 biomechanical proprieties assessed by FEA) had an added value in predicting fractures in a subgroup of women  
39 belonging to the Belgian FRISBEE cohort. [One](#) hundred nineteen women who sustained a fracture (aged 60 to  
40 85 years) during the initial follow-up of our cohort had a radius and tibia examination by HR-pQCT and were  
41 compared with controls matched for their FRAX score at baseline. We found that low distal radius total (OR=  
42 1.41 [1.07-1.86] per SD,  $p < 0.05$ ) and trabecular densities (OR= 1.45 [1.10-1.90],  $p < 0.01$ ), trabecular number (OR=  
43 1.32 [1.01-1.72],  $p < 0.05$ ), intra individual distribution of separation (OR= 0.73 [0.54-0.99],  $p < 0.05$ ) as several FEA  
44 parameters were significantly associated with fractures. At the distal tibia, impaired cortical density (OR= 1.32  
45 [1.03-1.70] per SD,  $p < 0.05$ ) and thickness (OR= 1.29 [1.01-1.63],  $p < 0.05$ ) and apparent modulus (OR= 1.30 [1.01-  
46 1.66],  $p < 0.05$ ) were significantly correlated with fractures. A low ultra distal radial aBMD (UDR) measured at  
47 the time of HR-pQCT was significantly associated with fractures (OR= 1.67 [1.22-2.28],  $p < 0.01$ ). Women from  
48 both groups were followed further after the realisation of the HR-pQCT and 46 new fractures were registered. In  
49 this second part of the study, low UDR aBMD (OR= 1.66 [1.18-2.35],  $p < 0.01$ ), total (OR= 1.48 [1.08-2.03],  $p < 0.05$ ),  
50 cortical (OR= 1.40 [1.04-1.87],  $p < 0.05$ ) and trabecular (OR= 1.37 [1.01-1.85],  $p < 0.05$ ) densities or apparent modulus  
51 (OR= 1.49 [1.07-2.05],  $p < 0.05$ ) at the radius were associated with a significant increase of fracture risk. At the  
52 tibia, only the cortical density was significantly associated with the fracture risk (OR= 1.34 [1.02-2.76],  $p < 0.05$ ).  
53 These results confirm the interest of HR-pQCT measurements for the evaluation of fracture risk, also in women  
54 matched for their baseline FRAX score. They also highlight that UDR aBMD contains pertinent information.

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57 **Key words:** osteoporosis; fracture prediction; HR-pQCT; FRISBEE; FRAX; UDR aBMD

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## 62 1. Introduction

63  
64 Osteoporosis (OP) is a condition characterized by loss of bone mass and bone micro-architectural  
65 deteriorations leading to an increased bone fragility and occurrence of fractures [1]. The mechanical properties  
66 of bone tissue and the osseous resistance depend on bone mass and bone quality - a complex notion which refers  
67 to a combination of micro-architecture, accumulated microscopic damage, collagen maturity and biomechanical  
68 modifications, the degree of mineralization, mineral crystal size, non-collagenous proteins and bone turnover [2].  
69 Both bone mass and quality deteriorate with ageing. With increasing life expectancy, the growing size of the  
70 ageing population raises the burden of osteoporotic fractures (OFs) and makes it necessary to develop cost-  
71 effective screening techniques to identify individuals at high risk of fracture in order to provide them an early  
72 and appropriate treatment.

73  
74 The operational diagnosis of OP is based on the measurement of areal bone mineral density (aBMD) by  
75 dual-energy X-ray absorptiometry (DXA) and defined by a T-score value more than or equal to 2.5 standard  
76 deviations (SD) below the young healthy adult mean at lumbar spine, femoral neck or total hip [1]. This classical  
77 definition does not allow an optimal risk prediction since more than half of OFs occur in postmenopausal women  
78 classified as osteopenic or with normal BMD [3]. The risk ascribable to bone density in subjects with a fragility  
79 fracture is lower than 50% [4]. A better prediction of OFs should also take into account factors reflecting bone  
80 architecture and biomechanical alterations. These are in part determined by several clinical risk factors (CRFs),  
81 such as age, low BMI, corticosteroid therapy, a prior fragility fracture or a parental hip fracture history, which  
82 are associated with fracture risk independently of BMD [5].

83  
84 These CRFs, alone or in association with BMD, have been combined to construct different models to calculate  
85 OFs probabilities at 5 and 10 years [5]. The most widely used is the FRAX score, which is based on a set of ten  
86 CRFs with or without BMD measurement and provides a 10-year probability to sustain a major osteoporotic  
87 fracture (MOF: forearm, shoulder, clinical spine or hip fracture) or a hip fracture. This user-friendly online  
88 algorithm has largely proven its ability to improve the fracture prediction with regards to BMD alone, resulting  
89 in a better selection of patients requiring a treatment on the basis of a threshold fracture risk, for instance a 10  
90 year risk above 20% for MOFs [7].

91 Besides, some micro-architectural parameters not included in aBMD measured by DXA could be associated with  
92 fracture risk, independently of aBMD. High-resolution peripheral quantitative computed tomography (HR-

93 pQCT) has been developed to get insights into bone micro-architecture. It provides a quantitative 3D assessment  
1 94 of the volumetric BMD (vBMD) for the cortical and trabecular compartments. Owing to a high resolution, it  
2  
3 95 allows the evaluation of cortical porosity and indices of trabecular micro-architecture. The data obtained with  
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5 96 HR-pQCT also allow a micro-finite element analysis ( $\mu$ FEA) of bone strength [8].  
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7 97 Multiple cross-sectional and several prospective studies have shown an association of some HR-pQCT  
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9 98 parameters with the presence of prevalent fractures or the risk of incident fractures in men and women, persisting  
10  
11 99 after adjustment for CRFs or hip aBMD [9–11].  
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13 100  
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15 101 The Fracture RiSk Brussels Epidemiological Enquiry (FRISBEE) study is a large population-based  
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17 102 cohort study evaluating risk factors for osteoporotic fractures in post-menopausal Belgian women [12]. We used  
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19 103 this cohort to evaluate in an ancillary study the impact of HR-pQCT parameters on fracture risk. Bone quality  
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21 104 was evaluated by HR-pQCT in a sub-group of FRISBEE volunteers who fractured after inclusion in the study  
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23 105 and was compared to that of women with similar FRAX score at baseline but who did not fracture during the  
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25 106 same follow-up period. Both groups were then followed for several years to evaluate if HR-pQCT is a useful  
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27 107 predictor of OFs, independently of FRAX or aBMD.  
28

## 29 108 30 31 109 32 33 110 **2. Study population and methods** 34 35 36 111 37

38 112 This study is a case-control study nested in the FRISBEE project that has been described elsewhere [12].  
39  
40 113 Briefly, 3560 postmenopausal women, aged between 60 and 85 years, living in the Brussels' area were recruited  
41  
42 114 between July 2007 and June 2013. Their CRFs for OP or fracture were recorded at baseline and are reevaluated  
43  
44 115 each year by telephone contact. All women underwent a spine and hip aBMD measurement at inclusion.  
45  
46 116 Fractures occurring during follow-up were registered and systematically validated by radiological  
47  
48 117 documentation.  
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### 50 118 51 52 119 **2.1 Participants selection** 53

54 120 To ensure a minimum follow-up period of three years, only the first 1740 women included in the  
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56 121 FRISBEE cohort before July 2010 were considered in the present study (Fig. 1). In July 2013, 188 of them had  
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58 122 sustained at least one fragility fracture (for a total of 225 fractures as some participants presented multiple  
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60 123 fractures). Between August 2013 and September 2014, these 188 women were re-invited for a quantitative and  
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124 qualitative assessment of their bone architecture by HR-pQCT, for a reevaluation of their CRFs and the  
1 125 realization of a second DXA, including a radius aBMD measurement. One hundred and nineteen accepted to  
2 participate. Reasons for non-participation of the 69 women with OFs were: refusal to take part at the  
3 126 investigation for medical reasons or age (31), death (10), lost to follow-up (8), recent investigation by their GP,  
4 127 remoteness or missed appointments (20). For each fracture case who accepted to participate, two controls,  
5 128 matched for their baseline FRAX score, were randomly selected among the sub-group of 1740 women who were  
6 129 similarly reevaluated (HR-pQCT, DXA, CRFs). In order to obtain unbiased estimates of relative risk, controls  
7 130 have been selected by incidence density sampling, using the macro developed by Richardson [13]. This method  
8 131 involves matching each fractured woman (case) to a sample of those with similar risk who had not already  
9 132 fractured at the time of case occurrence (selection without replacement). In other words, women with a fracture  
10 133 could be selected as control, as long as they had not fractured. For example, a woman, included in the study in  
11 134 September 2007, who fractured in August 2009 (time to fracture = 2 years) can be considered as a control for  
12 135 any other participant who fractured less than 2 years after her inclusion in FRISBEE (whatever the date of this  
13 136 inclusion). This was the case of 24 participants. As HR-pQCT measurements were performed in more subjects  
14 137 than were necessary for defining the control group, a total of 417 evaluations were available. All these 417  
15 138 participants were followed up and fractures that occurred after the HR-pQCT assessment were registered with  
16 139 the endpoint being the first fracture occurring after the HR-pQCT assessment. This design allowed a hindsight of  
17 140 5.2 ± 0.9 yrs between the inclusion and the realization of the HR-pQCT and a follow-up of 3.6 ± 0.7 yrs after the  
18 141 HR-pQCT (September 2018 evaluation).

142

143  
144 All procedures were approved by the CHU-Brugmann Hospital ethical committee and participant consent was  
145 obtained before study initiation (approval number B07720072493).

146

## 147 2.2 Clinical risk factor data collection - questionnaire and clinical assessments

148 At baseline, all women answered a standardized questionnaire that has been previously described [12].

149 The following clinical and historical data were collected for each subject: age, BMI, age at menopause, self-  
150 reported personal history of low-trauma fracture after 50 yrs, history of parental hip fracture, corticosteroid use  
151 for more than 3 months, current smoking or excessive alcohol intake ( $\geq 3$  units/day) and chronic diseases known  
152 to be causes of secondary osteoporosis. Risk factors not considered in the FRAX model were also collected:  
153 notably, a history of falls during the last year, a sedentary lifestyle (defined as < 30 minutes of light activity per  
154 day, e.g walking, carrying light loads, bicycling) [12,14], a simple muscle strength evaluation (evaluated by the

155 'sit-to-stand test' [15]), the use of sleeping pills (benzodiazepines), proton pump inhibitors, selective serotonin  
1 156 reuptake inhibitors and the socio-economic level. Hormone replacement therapy, calcium and vitamin D  
2  
3 157 supplementation or specific treatments for OP were also registered.  
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### 7 159 **2.3 FRAX score calculation**

9 160 BMD-FRAX score at inclusion was calculated for each participant, using the web application, available  
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11 161 at <http://www.shef.ac.uk/FRAX/>, on the basis of the different CRFs registered at baseline including BMD at the  
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13 162 femoral neck. Women with fractures(s) and controls were matched according to their probability of MOFs, with  
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15 163 a tolerance of  $\pm 1\%$  for FRAX scores  $\leq 20\%$ ,  $\pm 3\%$  above 20% and up to  $+ 8\%$  above 30% (we systematically  
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17 164 selected controls with superior FRAX scores in that category). New FRAX scores with BMD were calculated  
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19 165 after the second evaluation considering the modifications of the CRFs and the changes in BMD.  
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### 23 167 **2.4 Fracture ascertainment**

25 168 Only the incident fractures that occurred with minimal or no trauma during follow-up were registered.  
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27 169 Fingers, toes, skull and face fractures were not considered. In addition to the MOFs considered in the FRAX  
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29 170 model (hip, shoulder, vertebra, wrist), ankle, pelvis, sacrum, elbow, humerus, tibia, scapula, femur and radius  
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31 171 fractures were also considered as "other major" fractures in the Frisbee study, as they can directly impact subject  
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33 172 morbidity or mortality [16]. If a participant sustained more than one fracture during the follow-up, only the first  
34  
35 173 one was taken into account. All fractures were confirmed by radiographs or surgical reports.  
36

37 174

### 39 175 **2.5 Bone mineral density and bone micro-architecture measurements**

41 176 Lumbar spine (LS), total hip (TH) and femoral neck (FN) areal bone mineral density (aBMD, g/cm<sup>2</sup>)  
42  
43 177 was measured using dual energy X-ray absorptiometry (Hologic System 4500W) following conventional  
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45 178 procedures. Ultra distal radius aBMD (UDR aBMD) was measured once at the time of the HR-pQCT.  
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47 179 Volumetric density and bone micro-architecture were assessed by HR-pQCT (XtremeCT I; Scanco Medical AG,  
48  
49 180 [enabling a nominal resolution or voxel size of 82µm](#)) according to the manufacturer's standard in vivo  
50  
51 181 acquisition protocol ([effective energy of 60 kVp, x-ray tube current of 95 mA and matrix size of 1536x1536](#)).  
52  
53 182 Non-dominant distal radius and distal tibia were investigated (if a previous distal radius or tibia fracture was  
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55 183 reported, the opposite limb was scanned). Region of interest (ROI) at the radius consisted of a 9 mm length of  
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57 184 bone located from 9.5 to 18.5 mm proximal to the [midjoint line of the endplate](#); at the tibia, it was located from  
58  
59 185 [22.5 to 31.5 mm proximal to the tibial extremity](#) [17,18]. [The choice of a fixed offset distance to define the ROI](#)  
60



186 rather a relative position scaled to the individual bone length yields ~2% and ~6% error measurement for tibia  
1 187 and radius, respectively [19]. Such uncertainties are significantly lower than the observed inter-individual  
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3 188 variability in our cohort. HR- pQCT outcomes included: total, cortical and trabecular volumetric bone density  
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5 189 (Tt.vBMD, Ct.vBMD and Tb.vBMD, mgHA/cm<sup>3</sup>); cortical thickness (Ct.Th,  $\mu$ m, direct method [20]) and  
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7 190 porosity (Ct.Po, %); trabecular number (Tb.N, mm<sup>-1</sup>), thickness (Tb.Th; mm), separation (Tb.Sp; mm) and intra  
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9 191 individual distribution of separation (Tb.Sp.SD, mm). HR-pQCT precision errors (expressed as CV) vary from  
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11 192 less than 1.5% for density measurements to 4.5% for structural parameters [18]. All scans were scored for  
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13 193 motion artifact on a scale of 0 (no artifact) to 4 (significant blurring, cortical discontinuities or streaking): grade  
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15 194 4 images were excluded [21].  
16

## 19 196 2.6 Finite element analysis (FEA)

21 197 FE models were generated using Image Processing Language (IPL) software provided by Scanco  
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23 198 Medical. Material properties were chosen isotropic and elastic. Cortical and trabecular bone elements were  
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25 199 assigned a Young's modulus of 20 and 17 GPa, respectively [22]. We considered the following FEA-derived  
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27 200 variables: the percentage of load carried by the trabecular and cortical bone at the distal and proximal surface of  
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29 201 the volume of interest (Tb.Dist.Load, Tb.Prox.Load, Ct.Dist.Load and Ct.Prox.Load, %, respectively), the  
30  
31 202 average and SD values of the Von Mises stresses in the trabecular and cortical bone (Tb.Av.Stress and  
32  
33 203 Ct.Av.Stress; Tb.SD.stress and Ct.SD.stress, MPa, respectively), the stiffness (kN/mm), the apparent modulus  
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35 204 and the estimated failure load (N).  
36

## 39 206 2.7 Statistical analyses

41 207 Student's t-tests were used to compare densities, microarchitecture, and mechanical parameters of  
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43 208 women in the 2 groups. For the nested case control analysis, odds ratio estimates (OR) with their 95% CI were  
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45 209 obtained using conditional logistic regressions which consider subject matching. Because of the method of  
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47 210 controls selection (without replacement from all persons at risk at the time of case occurrence), the sample used  
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49 211 is representative of the full cohort and OR should be interpreted as hazard ratios (HR) [23]. Univariate and  
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51 212 bivariate (adjustment for OP treatment at the time of HR-pQCT) analysis were conducted.

53 213 For the 417 patients followed up after HRpQCT, relative risk estimates with their 95% CI were obtained using  
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55 214 Cox model, the endpoint being the first fracture occurring after the HR-pQCT assessment. Each parameter was  
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57 215 transformed in SD units in order to express outcomes as ORs or HRs per 1 SD diminution. To gain a better  
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59 216 understanding of the interrelationship among highly correlated HR-pQCT parameters, we also conducted in both  
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217 parts a principal component analysis (PCA) for the radius and the tibia separately after standardization of the  
218 variables. Very simply, PCA transforms the original interrelated variables into a new set of uncorrelated  
219 variables called Principal Components (PCs) (e.g. [24]). PCs are linear combinations of the original variables  
220 which represent most of the variance of the dataset. Each PC can be interpreted on the basis of the weight of the  
221 initial variables. Finally, as these PCs are uncorrelated, they were used in multivariate analysis as predictor of  
222 fracture. In the nested case control part, a multivariate conditional logistic analysis was performed using a  
223 backward selection model with a p-value cut-off of 0.05. In the second part, we used a Cox model and a  
224 backward selection of the PCs with a p-value cut-off of 0.05. All significance probabilities are for two-sided  
225 tested and we set the threshold for significance at  $p < 0.05$ .

### 228 3. Results

#### 230 3.1 Fractures

##### 232 3.1.1 First part (fractures which occurred before HR-pQCT)

233 The main sites of the 225 fractures (including multiple fractures) were the wrist (25.7%), the spine (16.0%), the  
234 shoulder (15.1%), the ankle (10.7%) and the hip (9.0%). Out of the 188 considered fractures, 127 were defined  
235 as MOFs according to the FRAX model, 34 as “other major” fractures and 27 as minor fractures. Out of the 119  
236 fractures of the HR-pQCT group, 71 were defined as MOFs (8 hips, 16 shoulders, 36 wrists, 11 vertebrae), 23 as  
237 “other major” fractures and 25 as minor fractures. The mean time to first fracture was  $2.7 \pm 1.7$  yrs [5 days - 6.2  
238 yrs]. All fracture types and numbers are summarized in Table 1.

##### 240 3.1.2 Second part (fractures which occurred after HR-pQCT)

241 Forty six subjects (30 initially control women and 16 already fractured women) fractured after the HR-pQCT  
242 evaluation. Thirty nine of these fractures were defined as MOFs (6 hips, 9 shoulders, 10 wrists, 14 vertebrae)  
243 according to the FRAX definition and six as “other major” fractures. New incident fractures occurred  $2.2 \pm 1.1$   
244 yrs [18 days – 4.4 yrs] after the second evaluation date (Table 1).

#### 246 3.2 BMD and HR-pQCT

248 **3.2.1** First part (fractures which occurred before HR-pQCT, n=119)

1 249 Thirty radius and eight tibiae scans had to be excluded because of poor quality. The percentage of rejected scans  
2  
3 250 did not differ significantly between the fracture and control groups.

4  
5 251 According to the study design, women with incident fractures after inclusion in FRISBEE did not differ from  
6  
7 252 FRAX-matched controls for the main CRFs included in the FRAX. As expected, FN aBMD was similar in the  
8  
9 253 two groups. On the contrary, ultra distal radial aBMD measured at inclusion in the sub-study was significantly  
10  
11 254 lower in the fractured group (Fx) (Table 2, left part).

12  
13 255 As shown in Table 2, there were statistically significant differences between control and fractured women for  
14  
15 256 several micro-architectural parameters. Fracture cases had lower total and trabecular densities ( $p=0.02$  and  $0.01$   
16  
17 257 respectively) and higher Tb.Sp SD ( $p=0.05$ ) at the radius. At the tibia, women with fractures had lower cortical  
18  
19 258 density, thickness and higher porosity ( $p=0.01$ ,  $0.01$  and  $0.04$ , respectively) than controls.

20  
21 259 Concerning biomechanical parameters: at the radius, both trabecular and cortical SD stresses were higher  
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23 260 ( $p=0.02$ ) in Fx vs non-Fx. Cortical SD stresses were also higher at the tibia ( $p<0.01$ ). Apparent modulus and  
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25 261 estimated failure load were significantly lower at the distal radius ( $p=0.001$  and  $0.05$ ) and tibia ( $p<0.01$  and  
26  
27 262  $0.03$ ). Women with fractures had lower stiffness at the tibia ( $p=0.01$ ).

28  
29 263 At the radius, each SD decrease of Tt.vBMD, Tb.vBMD, Tb.N, Tb.Sp.SD, Trab and Cort.SD.Stress, stiffness,  
30  
31 264 app. modulus and failure load values was significantly associated with fractures ( $p<0.05$ ). The association  
32  
33 265 remained significant after adjusting for treatment, except for Tb.N. At the distal tibia, each SD decrease of the  
34  
35 266 value of Ct.vBMD, Ct.Th and app. modulus was significantly associated with fractures even after adjusting for  
36  
37 267 treatment ( $p<0.05$ ) (Table 2. right part).

38  
39 268

40  
41 269 **3.2.2** Second part (fractures which occurred after HR-pQCT)

42  
43 270 Table 3 shows the follow-up results of the 417 women included in this sub-study (37 radius and 11 tibiae scans  
44  
45 271 excluded because of poor quality, no difference of percentage of rejected scans between the two groups). No  
46  
47 272 matching for FRAX was realized for this analysis. Women who sustained incident Fx after HR-pQCT had  
48  
49 273 significantly lower density parameters (Tt.vBMD, Tb.vBMD) at the radius ( $p=0.02$  and  $0.04$  respectively), while  
50  
51 274 no significant difference was observed in structural parameters at the tibia. Ultra distal radial (UDR) aBMD was  
52  
53 275 also significantly lower in the fractured group ( $p<0.01$ ). FEA showed only a significant difference in the radial  
54  
55 276 apparent modulus between Fx and non-Fx women ( $p=0.01$ ).

56  
57 277 In this second part, a decrease of aBMD, Tt.vBMD, Ct.vBMD, Tb.vBMD or app. modulus at the radius was  
58  
59 278 associated with a significant increase of fracture risk ( $p < 0.05$ ), even after adjusting for treatment (except for

279 Tb.vBMD). At the tibia, Ct.vBMD was the only parameter significantly associated with fracture risk. After  
1 280 adjustment for treatment or FRAX recalculated at inclusion into the sub-study, none of the HR-pQCT parameters  
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3 281 were still significantly predictive but UDR aBMD remained significantly associated with fracture risk.  
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### 7 283 3.2.3 Principal component analysis

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9 284 In the nested case-control study PCA, four principal components explaining at least 10% of the total variance  
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11 285 emerged for the radius and the tibia. Together they explained 91% and 86% of the total variability of our whole  
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13 286 set of bone characteristics parameters. For the follow-up, we found three (for the radius) and four (for the tibia)  
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15 287 principal components explaining at least 10% of the total variance and explaining 82% and 86% of the total  
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17 288 variability at the radius and the tibia, respectively. The correlations of each parameter with the PCs are presented  
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19 289 in Table 4, where the highest correlations are marked in bold. These correlations indicate the degree and  
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21 290 direction of each of the original variables' contribution to each component.

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23 291 In both PCAs, the composition of the first PC was quite similar at the radius and the tibia, regrouping the total  
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25 292 density (and aBMD for the radius) and several qualitative parameters (cortical and trabecular SD stresses,  
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27 293 cortical average stress, stiffness, apparent modulus and failure load). Only the first PC of the radius was  
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29 294 significantly associated with an increased fracture risk (HR 1.16 [1.04-1.28],  $p < 0.01$ ). This PC explained by  
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31 295 itself ~50% of the total variance for the radius. Again, the tibia was less predictive.

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## 37 298 **4. Discussion**

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42 300 In this Belgian study, we investigated the predictive value of HR-pQCT for osteoporotic fractures.  
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44 301 FRISBEE participants who sustained an incident fracture during the first five years of follow-up were compared  
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46 302 to women with similar initial FRAX score. To our knowledge, it is the first study where participants were  
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48 303 matched for their FRAX score at inclusion. This approach allows to examine whether HR-pQCT adds  
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50 304 information to bone fragility with regards to FRAX with BMD. Moreover, in the second part of the study, all  
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52 305 participants were monitored during an average follow-up of 3.6 yrs for the occurrence of fragility fractures.  
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56 307 In this cohort, only 35 out of the 188 women who sustained a fracture (19%) had a 10-year  
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58 308 probability of MOF  $\geq 20\%$  at baseline so that more than 80% of these would not have been taken into account  
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60 309 for treatment considering this fixed threshold (76% would not have been treated if BMD alone had been taken  
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310 into account). In countries where the threshold for therapy depends on age, these proportions are likely to vary,  
311 but a majority of patients would still not be treated. Sornay-Rendu and colleagues found in the OFELY study  
312 that approximately half of the women who sustained a fragility fracture were not identified as high risk by the  
313 FRAX score [25]. The same was true for the Manitoba cohort-based study or the Lausanne University Hospital  
314 study, reflecting that FRAX (and the different defined thresholds) is not always an optimal predictive criteria, as  
315 it is the case for BMD [26,27]. Additionally, almost 40% of the women who sustained a fracture (74/188) had an  
316 estimated fracture probability lower than 10% (low risk range). These figures and those from other retrospective  
317 or prospective cohorts suggest that the FRAX, just as BMD, underestimates the risk of fragility fractures [7].  
318 This observation is partially explained by the fact that the score does not consider some CRFs that might have an  
319 impact on fracture risk. History of falls and physical activity for example could be important [28].

320  
321 Bone strength first depends on bone density: this important factor explains, depending on the studies,  
322 between 60 and 80% of the variability of bone strength. However, the bone quality, a concept that describes  
323 aspects of bone composition and structure, also contributes to bone strength. There is thus room for possible  
324 improvement of fracture prediction, using additional quantitative parameters reflecting the bone structure and/or  
325 strength. Several studies suggest that HR-pQCT might outperform DXA in fracture risk prediction [10].  
326 Our nested case-control analysis showed that several structural and/or biomechanical parameters characterized  
327 those who suffered an incident fracture. This highlights the importance of the structural information. Greater  
328 impairments of the trabecular parameters (Tb.vBMD, TbN, Tb.Sp.SD) were observed at the radius of the  
329 fractured women while only cortical density, porosity and thickness were statistically associated with fractures at  
330 the tibia. The small number of hip fractures present in our sample may impact these results. However, such  
331 discrepancies according to the site of measurement were previously noted in other cross-sectional studies  
332 comparing HR-pQCT parameters in women with and without prevalent fractures [29,30]. It may be explained by  
333 the broader cortical thickness of the tibia and by the fact that the tibia, in contrast to the radius, is a weight-  
334 bearing bone and is hence exposed to other mechanical stimuli that differently impact the architectural  
335 parameters. This difference is also observed in FEA results: a majority of the bone resistance parameters were  
336 significantly associated with fractures at the radius, while only the apparent modulus differed significantly  
337 between the two groups at the tibia.

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339 In the second part of the study, fewer parameters were predictive for fractures. They were mainly  
340 density parameters (Tt.vBMD, Ct.vBMD, Tb.vBMD) and app. modulus at the radius and only D.cort at the tibia.

341 No association remained significant after adjustment for the FRAX score, which was significantly higher in the  
1 342 group of patients who sustained a fracture after the HR-pQCT. This can result from the valuable predictive  
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3 343 power of the FRAX tool. However this observation could also arise from an insufficient statistical power  
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5 344 resulting from a too small number of incident fractures. The 46 fractures observed during the prospective study  
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7 345 were indeed far below the total number of events needed considering the ORs of the retrospective part (i.e. 119  
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9 346 to 484 depending on the considered HR-pQCT parameter; <http://sample-size.net/sample-size-survival-analysis>  
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11 347 [31]). Nevertheless, the data of this subsequent analysis confirm our first conclusions, with both trabecular and  
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13 348 cortical densities lower at the radius when only the cortical density identifies those who will fracture at the tibia,  
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15 349 and the HRs of the follow up analysis are significantly correlated with the ORs of the nested case study (data not  
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17 350 shown). Moreover, the hazard ratios observed in our study are concordant with those of the large international  
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19 351 cohort recently described by Samelson et al, where the risk was increased by around 10 to 60% for 1 SD  
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21 352 decrease for each considered parameter [11] (Fig. 2). In that study, HRs were still significant after adjustment for  
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23 353 the FRAX.

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27 355 We did not find any association of cortical porosity at the radius or the tibia with fractures. The association  
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29 356 between this parameter and the occurrence of OFs is indeed quite variable in the literature depending on the  
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31 357 method used to define the zone of interest for the evaluation. For example, Kral and colleagues using a new more  
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33 358 inclusive algorithm (non-threshold-based software) found a correlation between the cortical porosity and the  
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35 359 prevalence of non vertebral fractures, independent of the FRAX score [32]. In contrast and unexpectedly, in the  
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37 360 GLOW study, history of fracture was associated with lower cortical porosities [30]. The synthesis of the various  
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39 361 prospective studies published by Samelson et al did not show any significant association between cortical  
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41 362 porosity and fracture risk [11]. The average great age of our cohort (~75 yrs at HR-pQCT assessment) could also  
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43 363 be an explanation: the fact that the majority of bone loss occurs in the cortical compartment after the age of 65  
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45 364 years could have led to bias toward null differences between our groups of participants [33].

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49 366 Additionally, our results do not indicate that failure load is an independent predictor for fracture (HR 1.22 [0.94-  
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51 367 1.58]). This is at odds with the BoMIC results [11]. Apart from an insufficient power due to the low rate of  
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53 368 fracture events in our cohort, this discrepancy could be explained by different methods for failure load  
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55 369 calculation, hampering adequate comparison of our results. In the BoMIC consortium, the used FEA conditions  
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57 370 are different from one cohort to another. Authors harmonized the data using a modulus of 6.829 GPa (while we  
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59 371 considered two modulus of 17 and 20 GPa for trabecular and cortical bone, respectively). Compared to the  
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372 BoMIC methodology, this leads to an increase of the Failure Load in our cohort [34] and therefore to a lower  
1 373 risk. When our results are compared to those of the OFELY and STRAMBO studies (2 cohorts included in the  
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3 374 BoMIC), that used the same approach than in Frisbee, the HRs were similar (HR 1.44 [1.21-1.72] and 1.79  
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5 375 [1.44-2.23], respectively [29,35])  
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9 377 Furthermore, considering that, for economic reasons, the assessment of the bone structure and/or  
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11 378 strength by HR-pQCT will not replace the systematic screening of fracture risk by DXA and/or FRAX in a  
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13 379 nearby future, we examined if specific groups could benefit from this method. Considering the subgroup of our  
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15 380 HR-pQCT cohort having a FRAX score < 20% (low and intermediate risk): we found in the second analysis that  
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17 381 the trabecular thickness of the radius discriminated participants with incident fractures (p=0.05, data not shown).  
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19 382 However, the small number of fractures in this ancillary study precludes drawing definitive conclusions.  
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21 383  
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23 384 Finally, it is of interest that UDR aBMD provides a lot of information. Significant risk gradient was  
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25 385 associated with this parameter both in the nested case and follow up part of the study, with a risk increase of  
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27 386 almost 66% per SD decrease. The fact that almost all HR-pQCT ORs were no longer significant after adjustment  
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29 387 for UDR aBMD supports this conclusion. This results from the strong correlation between the HR-pQCT  
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31 388 parameters and the UDR aBMD. Additionally, UDR aBMD is the only variable that is still significant after  
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33 389 adjusting for the FRAX score in the follow-up study, keeping in mind that the statistical power of the  
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35 390 prospective part is limited. In their prospective study, Biver et al also demonstrated a very good performance of  
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37 391 the UDR aBMD for fracture prediction (HR ~1.75) [36]. This good predictive power is probably explained by  
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39 392 the fact that UDR aBMD combines both trabecular and cortical bone and is thus a pertinent composite predictor  
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41 393 of bone strength.  
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43  
44 394 The strengths of our nested case-control study are that all fragility fractures were prospectively assessed  
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46 395 and X-ray verified, all CRFs were collected at baseline and confirmed each year by phone and at the time of HR-  
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48 396 pQCT measurements. A restriction of this analysis is the short delay between baseline and the second evaluation  
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50 397 ( $5.2 \pm 0.9$  yrs), while the FRAX predictions are based on a 10 year risk evaluation. Nevertheless, the design of  
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52 398 our study guarantees a similar follow-up duration for the Fx and the non-Fx groups. It is also relevant to note  
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54 399 that only 10% of the controls (30/298) had a subsequent fracture during the second period, so during a total  
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56 400 period of  $8.8 \pm 1.1$  yrs. In addition to the small number of fractures, the relatively short follow-up (median 3.6  
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58 401 yrs) of the prospective part of the study is another weakness because, which can explain that some of the  
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60 402 measured parameters were not predictive of fractures.  
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403 In conclusion, although HR-pQCT cannot be considered as a screening tool for now, it may be of  
1 404 interest in some subgroups. It is especially of major interest in the understanding of the biomechanical process of  
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3 405 fracture as well as the action of anti-osteoporotic treatments. Our results highlight the superiority of the radius  
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5 406 measurements in postmenopausal women and confirm the interest of the UDR aBMD that contains major  
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7 407 information on fracture risk. As follow-up is ongoing, a further prospective analysis of incident fractures is  
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9 408 planned.

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Figure 1 - Time line and follow-up of the cohort – Study design

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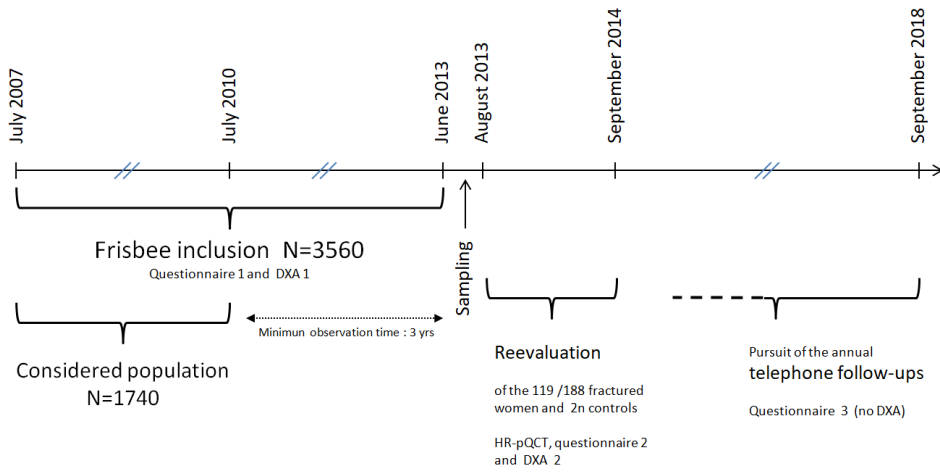
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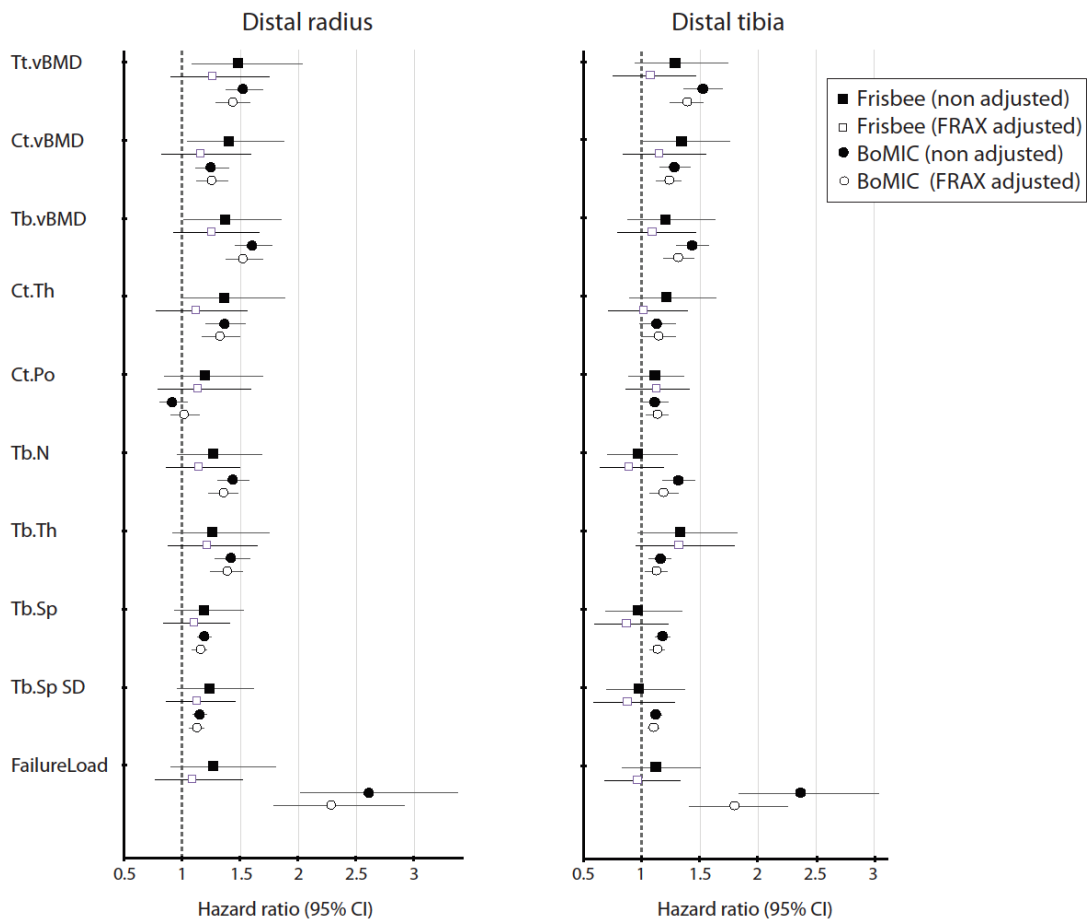
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Figure 2 - Comparison of our results with those of the BoMIC study (data extracted from [11], supplementary Table 2, women results)

Association between HR-pQCT indices and incidence of fractures. HRs are expressed per SD unit change in bone parameters in the expected direction of increased fracture risk. Shown error bars represent 95% confidence intervals.



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593 Table 1: Fractures distribution for Major Osteoporotic Fractures (MOF) according to FRAX and other fractures,  
 594 mean time to first fracture  
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Fractures		First part – before HR-pQCT					Second part – after HR-pQCT		
		Total women	With multiple fractures	Total fractures	Reevaluated women	With multiple fractures	Total women	Initial case women	Initial control women
	Total	188	37	225	119	20	46	16	30
MOFs FRAX	Hip	17	2	19	8	0	6	3	3
	Shoulder	29	5	34	16	3	9	3	6
	Wrist	53	5	58	36	5	10	5	5
	Vertebrae	28	8	36	11	3	14	3	11
Other major fractures	Pelvis	7	4	11	5	2	4	1	3
	Ankle	19	5	24	11	3	1	1	0
	Elbow	3	1	4	3	1	1	0	1
	Femur	0	1	1	0	0	0	0	0
	Tibia	1	2	3	1	1	0	0	0
	Humerus	1	0	1	1	0	0	0	0
	Sacrum	3	0	3	2	0	0	0	0
Non major fractures	Carpus	3	0	3	3	0	0	0	0
	Clavicle	1	0	1	1	0	0	0	0
	Ribs	4	2	6	4	0	0	0	0
	Metatarsus	12	2	14	11	2	0	0	0
	Metacarpus	0	0	0	0	0	1	0	1
	Patella	2	0	2	2	0	0	0	0
	Scapula	1	0	1	0	0	0	0	0
	Tarsus	4	0	4	4	0	0	0	0
MOFs FRAX	%	67.6	54.1	65.3	59.7	55.0	84.8	87.5	83.3
All major	%	85.6	89.2	86.2	79.0	90.0	97.8	100	96.7
Mean time to first fracture	Days	956±591 [5-2269]	-	-	973±619 [5-2269]	-	803±419 [18-1594]	817±482 [18-1594]	795±391 [51-1438]

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599 Table 2: HR-pQCT parameters of the women who fractured between inclusion and HR-QCT (Fx) and their  
 600 matched controls (C) (mean ± SD, OR [range])

	Fx (n=119)	C (n=238)	p	OR per ↓ 1 SD	OR adjusted for treatment	OR adjusted for UDRaBMD
Initial FRAX	12,6±6.7	12,6±6.7	NS	-	-	-
Age at baseline (yr)	70.7±6.3	69.9±6.2	NS	-	-	-
Age at HR-pQCT (yr)	76.5±6.3	75.2±6.1	NS	-	-	-
FN aBMD at baseline (g/cm <sup>2</sup> )	0.703±0.09	0.693±0.11	NS	-	-	-
FN aBMD at HR-pQCT (g/cm <sup>2</sup> )	0.668±0.09	0.667±0.09	NS	0.98 [0.71-1.35]	0.93 [0.66-1.30]	-
OP medication use	12.6%	21.8%	0.02			
<u>Radius</u>						
aBMD UDR mg/cm <sup>2</sup>	0.348±0.07	0.365±0.06	0.02	1.67 [1.22-2.28]**	1.63 [1.19-2.23]**	-
Tt.vBMD mg/cm <sup>3</sup>	263±58	280±69	0.02	1.41 [1.07-1.86]*	1.39 [1.05-1.84]*	1.66 [0.99-2.80]
Ct.vBMD mg/cm <sup>3</sup>	822±78	832±87	0.30	1.16 [0.89-1.50]	1.15 [0.88-1.49]	1.02 [0.70-1.49]
Tb.vBMD mg/cm <sup>3</sup>	126±39	138±44	0.01	1.45 [1.10-1.90]**	1.43 [1.08-1.89]*	1.29 [0.87-1.92]
Ct.Th μm	597±185	626±207	0.19	1.20 [0.92-1.57]	1.18 [0.90-1.55]	1.08 [0.70-1.68]
Ct.Po	69±6	68±6	0.13	0.83 [0.65-1.07]	0.84 [0.65-1.08]	0.76 [0.55-1.05]
Tb.N* mm-1	1.64±0.42	1.72±0.39	0.07	1.32 [1.01-1.72]*	1.29 [0.98-1.70]	1.05 [0.74-1.49]
Tb.Th μm	64±12	66±13	0.25	1.23 [0.94-1.62]	1.21 [0.92-1.60]	1.28 [0.88-1.87]
Tb.Sp μm	599±262	554±234	0.11	0.78 [0.59-1.03]	0.78 [0.59-1.04]	1.00 [0.69-1.44]
Tb.Sp SD μm	365±296	298±236	0.05	0.73 [0.54-0.99]*	0.74 [0.55-0.99]*	0.90 [0.62-1.31]
Trab.Prox.Load %	49±9	50±10	0.45	1.13 [0.87-1.47]	1.12 [0.86-1.46]	1.07 [0.78-1.47]
Trab.Dist.Load %	16.7±8.7	17.5±8.2	0.39	1.18 [0.91-1.53]	1.17 [0.90-1.51]	1.08 [0.81-1.46]
Trab.Av.Stress Mpa	8.2±1.7	8.1±1.7	0.72	0.90 [0.69-1.18]	0.92 [0.70-1.20]	1.15 [0.80-1.65]
Trab.SD.Stress Mpa	5.4±1.4	5.0±1.4	0.02	0.66 [0.49-0.89]**	0.67 [0.50-0.90]**	0.74 [0.47-1.17]
Cort.Av.Stress Mpa	16.4±3.9	15.9±3.8	0.21	0.91 [0.83-1.01]	0.92 [0.83-1.01]	0.98 [0.83-1.15]
Cort.SD.Stress Mpa	4.3±1.3	4.0±1.2	0.02	0.67 [0.50-0.88]**	0.68 [0.51-0.90]**	0.67 [0.44-1.02]
Stiffness kN/mm	116±28	122±27	0.06	1.55 [1.12-2.15]**	1.53 [1.10-2.14]*	1.41 [0.79-2.51]
App.Modulus	2802±631	3062±765	0.001	1.67 [1.24-2.25]***	1.65 [1.23-2.23]**	2.41 [1.43-4.08]**
Est.Failure.Load N	2774±665	2919±634	0.05	1.60 [1.14-2.23]**	1.58 [1.13-2.21]**	1.44 [0.82-2.25]
<u>Tibia</u>						
Tt.vBMD mg/cm <sup>3</sup>	227±50	237±48	0.07	1.21 [0.94-1.55]	1.20 [0.93-1.54]	1.23 [0.85-1.79]
Ct.vBMD mg/cm <sup>3</sup>	761±86	785±84	0.01	1.32 [1.03-1.70]*	1.33 [1.04-1.71]*	1.28 [0.94-1.73]
Tb.vBMD mg/cm <sup>3</sup>	144±34	146±36	0.59	1.04 [0.82-1.32]	1.01 [0.79-1.31]	0.91 [0.66-1.26]
Ct.Th μm	713±261	785±272	0.01	1.29 [1.01-1.63]*	1.29 [1.01-1.64]*	1.30 [0.96-1.77]
Ct.Po	105±16	103±8	0.04	0.79 [0.62-1.02]	0.79 [0.62-1.02]	0.66 [0.46-0.95]*
Tb.N* mm-1	1.7±0.4	1.7±0.4	0.36	0.90 [0.72-1.14]	0.88 [0.69-1.12]	0.82 [0.61-1.09]
Tb.Th μm	71±13	74±15	0.07	1.16 [0.92-1.46]	1.15 [0.91-1.46]	1.09 [0.82-1.46]
Tb.Sp μm	559±217	558±182	0.98	0.99 [0.78-1.25]	1.01 [0.79-1.29]	1.01 [0.75-1.34]
Tb.Sp SD μm	307±257	300±208	0.78	0.96 [0.77-1.21]	0.98 [0.78-1.24]	0.96 [0.73-1.28]
Trab.Prox.Load %	57±9.5	56±10.2	0.34	0.95 [0.76-1.18]	0.94 [0.75-1.17]	0.87 [0.68-1.12]
Trab.Dist.Load %	35±9.7	34±10.7	0.53	0.91 [0.73-1.11]	0.89 [0.71-1.12]	0.86 [0.66-1.11]
Trab.Av.Stress Mpa	4.0±1.3	3.9±1.1	0.28	0.91 [0.73-1.13]	0.92 [0.74-1.14]	0.96 [0.75-1.23]
Trab.SD.Stress Mpa	2.2±0.8	2.1±0.7	0.06	0.86 [0.68-1.08]	0.86 [0.68-1.09]	0.95 [0.72-1.25]
Cort.Av.Stress Mpa	7.3±2.5	6.9±2.0	0.18	0.89 [0.72-1.13]	0.91 [0.72-1.14]	0.98 [0.74-1.28]
Cort.SD.Stress Mpa	1.7±0.7	1.5±0.5	<0.01	0.79 [0.62-1.01]	0.79 [0.62-1.01]	0.84 [0.63-1.12]
Stiffness kN/mm	289±58	305±55	0.01	1.27 [0.98-1.66]	1.26 [0.97-1.65]	0.97 [0.68-1.39]

App.Modulus	3242±728	3451±704	<0.01	1.30 [1.01-1.66]*	1.29 [1.01-1.66]*	1.31 [0.94-1.82]
Est.Failure.Load N	7040±1244	7338±1269	0.03	1.22 [0.94-1.58]	1.21 [0.93-1.57]	0.93 [0.66-1.31]

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601 Significant levels: \* p<0.05, \*\* p<0.01, \*\*\* p<0.001



602 Table 3: HR-pQCT parameters of the women who fractured after HR-QCT (Fx) and controls (non-Fx) (mean  $\pm$   
 603 SD, HR [range])

	Fx (n=46)	Non-Fx (n=371)	p	HR per $\downarrow$ 1 SD	Adjusted for treatment	Adjusted for FRAX
FRAX at baseline	16.1 $\pm$ 10.2	11.4 $\pm$ 6.4	<0.01	-		
FRAX at HR-pQCT	19.3 $\pm$ 12.2	14.3 $\pm$ 7.1	<0.01	-		
Age at HR-pQCT	76.9 $\pm$ 5.7	74.7 $\pm$ 6.0	0.01	-		
OP medication use	30.4%	15.6%	<0.01	-		
FN aBMD 1 (g/cm <sup>2</sup> )	0.676 $\pm$ 0.11	0.709 $\pm$ 0.10	0.05	-		
FN aBMD 2 (g/cm <sup>2</sup> )	0.641 $\pm$ 0.09	0.677 $\pm$ 0.09	0.01	1.39 [0.98-1.98]	1.32 [0.92-1.91]	1.13 [0.75-1.71]
<u>Radius</u>						
aBMD UDR mg/cm <sup>2</sup>	0.336 $\pm$ 0.07	0.365 $\pm$ 0.06	<0.01	1.66 [1.18-2.35]**	1.63 [1.14-2.32]**	1.47 [1.02-2.13]*
Tt.vBMD mg/cm <sup>3</sup>	254 $\pm$ 68	280 $\pm$ 66	0.02	1.48 [1.08-2.03]*	1.41 [1.02-1.95]*	1.25 [0.90-1.75]
Ct.vBMD mg/cm <sup>3</sup>	808 $\pm$ 99	836 $\pm$ 78	0.09	1.40 [1.04-1.87]*	1.35 [1.00-1.81]*	1.14 [0.82-1.59]
Tb.vBMD mg/cm <sup>3</sup>	123 $\pm$ 41	137 $\pm$ 42	0.04	1.37 [1.01-1.85]*	1.29 [0.95-1.76]	1.24 [0.92-1.66]
Ct.Th $\mu$ m	574 $\pm$ 212	631 $\pm$ 194	0.08	1.36 [0.99-1.88]	1.30 [0.94-1.80]	1.10 [0.77-1.56]
Ct.Po	70 $\pm$ 7	68 $\pm$ 6	0.06	1.19 [0.84-1.69]	1.16 [0.82-1.65]	1.12 [0.79-1.59]
Tb.N* mm-1	1.6 $\pm$ 0.5	1.7 $\pm$ 0.4	0.14	1.27 [0.95-1.68]	1.20 [0.89-1.61]	1.13 [0.86-1.49]
Tb.Th $\mu$ m	63 $\pm$ 13	66 $\pm$ 13	0.12	1.26 [0.91-1.75]	1.20 [0.86-1.67]	1.20 [0.87-1.64]
Tb.Sp $\mu$ m	597 $\pm$ 259	554 $\pm$ 223	0.26	0.84 [0.66-1.08]	0.87 [0.67-1.13]	0.92 [0.71-1.20]
Tb.Sp SD $\mu$ m	354 $\pm$ 271	304 $\pm$ 245	0.33	0.81 [0.62-1.05]	0.83 [0.63-1.09]	0.90 [0.69-1.17]
Trab.Dist.Load %	49 $\pm$ 9	49 $\pm$ 10	0.74	1.18 [0.77-1.44]	1.03 [0.76-1.39]	1.15 [0.85-1.55]
Trab.Prox.Load %	16 $\pm$ 8	17 $\pm$ 8	0.48	1.11 [0.80-1.53]	1.07 [0.78-1.48]	1.18 [0.88-1.59]
Trab.Av.Stress Mpa	8.3 $\pm$ 1.6	8 $\pm$ 1.8	0.45	0.89 [0.65-1.22]	0.93 [0.68-1.27]	1.05 [0.78-1.43]
Trab.SD.Stress Mpa	5.5 $\pm$ 1.5	5 $\pm$ 1.4	0.05	0.77 [0.58-1.02]	0.81 [0.58-1.016]	0.88 [0.67-1.17]
Cort.Av.Stress Mpa	17 $\pm$ 4	16 $\pm$ 4	0.12	0.93 [0.84-1.03]	0.95 [0.85-1.05]	0.97 [0.838-1.08]
Cort.SD.Stress Mpa	4.4 $\pm$ 1.4	4 $\pm$ 1.2	0.08	0.79 [0.60-1.04]	0.83 [0.63-1.10]	0.90 [0.68-1.21]
Stiffness kN/mm <sup>2</sup>	114 $\pm$ 28	120 $\pm$ 27	0.13	1.30 [0.92-1.85]	1.22 [0.85-1.74]	1.09 [0.77-1.55]
App.Modulus	2740 $\pm$ 720	3032 $\pm$ 732	0.01	1.49 [1.07-2.05]*	1.42 [1.02-1.97]*	1.30 [0.92-1.84]
Est.Failure.Load N	2736 $\pm$ 634	2882 $\pm$ 638	0.17	1.27 [0.90-1.80]	1.18 [0.83-1.69]	1.07 [0.76-1.52]
<u>Tibia</u>						
Tt.vBMD mg/cm <sup>3</sup>	228 $\pm$ 60	239 $\pm$ 47	0.24	1.28 [0.95-1.74]	1.28 [0.948-1.742]	1.06 [0.76-1.47]
Ct.vBMD mg/cm <sup>3</sup>	757 $\pm$ 97	784 $\pm$ 78	0.08	1.34 [1.02-1.76]*	1.31 [0.99-1.72]	1.14 [0.84-1.55]
Tb.vBMD mg/cm <sup>3</sup>	142 $\pm$ 36	148 $\pm$ 34	0.28	1.20 [0.89-1.63]	1.10 [0.81-1.51]	1.08 [0.79-1.47]
Ct.Th $\mu$ m	741 $\pm$ 337	792 $\pm$ 258	0.34	1.21 [0.90-1.63]	1.18 [0.87-1.59]	1.00 [0.72-1.39]
Ct.Po	104 $\pm$ 9	103 $\pm$ 11	0.32	0.90 [0.73-1.11]	0.89 [0.72-1.09]	0.90 [0.71-1.15]
Tb.N* mm-1	1.7 $\pm$ 0.4	1.7 $\pm$ 0.4	0.94	0.96 [0.71-1.31]	0.90 [0.66-1.22]	0.88 [0.65-1.19]
Tb.Th $\mu$ m	71 $\pm$ 13	74 $\pm$ 13	0.13	1.33 [0.97-1.82]	1.29 [0.94-1.77]	1.31 [0.95-1.80]
Tb.Sp $\mu$ m	548 $\pm$ 168	553 $\pm$ 186	0.85	1.04 [0.74-1.45]	1.14 [0.80-1.63]	1.16 [0.81-1.67]
Tb.Sp SD $\mu$ m	290 $\pm$ 156	296 $\pm$ 221	0.82	1.02 [0.73-1.44]	1.12 [0.78-1.60]	1.15 [0.78-1.69]
TrabDistLoad %	57 $\pm$ 10	56 $\pm$ 10	0.81	0.99 [0.73-1.32]	0.96 [0.72-1.28]	1.07 [0.80-1.44]
TrabProxLoad %	35 $\pm$ 12	34 $\pm$ 10	0.47	0.89 [0.67-1.21]	0.88 [0.66-1.18]	0.99 [0.74-1.33]
TrabAvStress Mpa	4 $\pm$ 1.7	3.9 $\pm$ 1.3	0.69	0.96 [0.74-1.26]	1.00 [0.76-1.31]	1.03 [0.76-1.39]
TTrabSDStress Mpa	2.2 $\pm$ 0.9	2.1 $\pm$ 0.8	0.25	0.86 [0.67-1.10]	0.89 [0.69-1.15]	0.91 [0.69-1.19]
CortAvStress Mpa	7.3 $\pm$ 2.7	7 $\pm$ 2.4	0.44	0.90 [0.70-1.17]	0.94 [0.72-1.22]	0.96 [0.72-1.27]
CortSDStress Mpa	1.7 $\pm$ 0.7	1.6 $\pm$ 0.6	0.15	0.83 [0.65-1.06]	0.85 [0.66-1.10]	0.90 [0.68-1.18]
Tstiffness kN/mm <sup>2</sup>	297 $\pm$ 62	304 $\pm$ 55	0.45	1.15 [0.85-1.55]	1.08 [0.78-1.46]	0.97 [0.69-1.37]

App.Modulus	3278±913	3465±700	0.20	1.34 [0.98-1.83]	1.28 [0.93-1.76]	1.31 [0.81-1.58]
EstFailureLoad N	7198±1410	7346±1250	0.47	1.12 [0.83-1.50]	1.05 [0.76-1.44]	0.95 [0.68-1.33]

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Significant levels: \* p<0.05, \*\* p<0.01, \*\*\* p<0.001

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606 Table 4: PCA on nested case study (NC, left columns) and follow up (FU, right columns) at radius and tibia.

Component of variables	Radius								Tibia							
	PC 1		PC 2		PC 3		PC4		PC1		PC2		PC3		PC4	
	NC	FU	NC	FU	NC	FU	NC	FU	NC	FU	NC	FU	NC	FU	NC	FU
aBMD	<b>0.26</b>	<b>0.27</b>	0.06	0.03	0.05	0.06	0.11	-	0.19	0.19	0.07	0.06	0.16	0.18	0.04	0.08
Tt.vBMD	<b>0.26</b>	<b>0.27</b>	0.12	0.10	<b>0.28</b>	<b>0.28</b>	0.08	-	<b>0.29</b>	<b>0.30</b>	0.17	0.17	<b>0.25</b>	<b>0.26</b>	0.00	0.06
Ct.vBMD	0.17	0.20	<b>0.34</b>	<b>0.33</b>	0.12	0.10	0.13	-	0.14	0.19	<b>0.35</b>	<b>0.33</b>	0.04	0.02	0.16	0.17
Tb.vBMD	0.24	0.23	<b>0.25</b>	<b>0.27</b>	0.21	0.24	0.00	-	<b>0.28</b>	<b>0.25</b>	0.17	0.17	<b>0.26</b>	<b>0.32</b>	0.12	0.21
Ct.Th	0.20	0.23	<b>0.31</b>	<b>0.30</b>	0.12	0.11	0.00	-	0.17	0.22	<b>0.38</b>	<b>0.36</b>	0.11	0.07	0.11	0.10
Ct.Po	-0.04	0.06	0.21	0.22	<b>0.52</b>	<b>0.52</b>	0.11	-	0.02	0.05	0.21	<b>0.26</b>	0.21	0.16	0.04	0.08
Tb.N	0.19	0.18	<b>0.27</b>	<b>0.30</b>	0.00	0.02	<b>0.37</b>	-	0.18	0.17	0.24	0.24	0.20	<b>0.32</b>	<b>0.35</b>	<b>0.28</b>
Tb.Th	0.17	0.17	0.08	0.09	<b>0.34</b>	<b>0.38</b>	<b>0.44</b>	-	0.13	0.11	0.07	0.08	0.11	0.02	<b>0.59</b>	<b>0.62</b>
Tb.Sp	-0.17	0.17	<b>0.27</b>	<b>0.31</b>	0.01	0.03	<b>0.41</b>	-	0.20	0.19	<b>0.25</b>	0.25	0.20	<b>0.33</b>	<b>0.34</b>	<b>0.26</b>
Tb.Sp SD	-0.17	0.16	<b>0.25</b>	<b>0.28</b>	0.01	0.04	<b>0.43</b>	-	0.19	0.18	0.22	0.22	0.17	<b>0.29</b>	<b>0.34</b>	<b>0.27</b>
Trab.Dist.Load	0.07	0.05	<b>0.40</b>	<b>0.41</b>	0.06	0.11	0.23	-	0.05	0.01	<b>0.40</b>	<b>0.40</b>	0.03	0.08	<b>0.27</b>	<b>0.31</b>
Trab.Prox.Load	0.07	0.05	<b>0.40</b>	<b>0.42</b>	0.02	0.02	0.24	-	0.07	0.02	<b>0.39</b>	<b>0.40</b>	0.04	0.01	<b>0.26</b>	<b>0.28</b>
Trab.Av.Stress	-0.18	0.20	0.16	0.13	<b>0.42</b>	<b>0.44</b>	0.17	-	0.22	0.24	0.05	0.14	<b>0.40</b>	<b>0.34</b>	0.21	0.25
Trab.SD.Stress	<b>-0.29</b>	<b>0.29</b>	0.01	0.04	0.17	0.15	0.08	-	<b>0.28</b>	<b>0.29</b>	0.04	0.13	<b>0.36</b>	<b>0.33</b>	0.04	0.00
Cort.Av.Stress	<b>-0.28</b>	<b>0.28</b>	0.02	0.02	0.21	0.20	0.08	-	<b>0.26</b>	<b>0.27</b>	0.06	0.15	<b>0.38</b>	<b>0.34</b>	0.02	0.02
Cort.SD.Stress	<b>-0.27</b>	<b>0.28</b>	0.10	0.07	0.13	0.11	0.07	-	<b>0.27</b>	<b>0.30</b>	0.08	0.02	<b>0.36</b>	<b>0.34</b>	0.02	0.06
Stiffness	<b>0.27</b>	<b>0.28</b>	0.06	0.10	0.18	0.17	0.17	-	<b>0.32</b>	<b>0.34</b>	0.06	0.00	0.08	0.06	0.11	0.13
App.Modulus	<b>0.25</b>	<b>0.26</b>	0.18	0.02	0.22	0.23	0.09	-	<b>0.24</b>	<b>0.27</b>	<b>0.29</b>	<b>0.28</b>	0.15	0.11	0.13	0.17
Failure Load	<b>0.27</b>	<b>0.28</b>	0.03	0.00	0.20	0.19	0.17	-	<b>0.32</b>	<b>0.34</b>	0.04	0.02	0.07	0.07	0.07	0.09
Percentage of variance	50.0	50.1	22.8	22.0	10.2	10.1	7.7	-	37.2	37.2	23.5	23.5	14.6	14.6	10.8	10.8
		1.16	0.97	0.99	1.22	1.16	1.04	-	1.10	1.10	1.10	1.10	1.01	1.01	1.02	1.02
		[1.0	[0.8	[0.8	[0.9	[0.7	[0.8	-	[0.9	[0.9	[0.9	[0.9	[0.8	[0.8	[0.8	[0.8
		1.21	4-	5-	3-	9-	4-	3-	9-	9-	8-	8-	8-	8-	6-	6-
		[1.09-	1.28	1.12	1.18	1.50	1.54	1.30	1.22	1.22	1.24	1.24	1.17	1.17	1.21	1.21
HR		]	]	]	]	]	]	-	]	]	]	]	]	]	]	]
		0.000	0.00					-								
p-value		6	8	0.71	0.9	0.06	0.28	0.75	0.06	0.06	0.12	0.12	0.86	0.86	0.82	0.82

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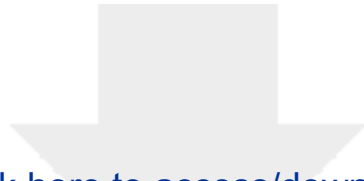
Fractures		First part – before HR-pQCT				Second part – after HR-pQCT		
		Total women	Multiple fractures		Reevaluated women	Total women	Initial case women	Initial control women
	Total	188	37 / 20	225	119	46	16	30
MOFs FRAX	Hip	17	2	19	8	6	3	3
	Shoulder	29	5 / 3	34	16	9	3	6
	Wrist	53	5 / 5	58	36	10	5	5
	Vertebrae	28	8 / 3	36	11	14	3	11
Other major fractures	Pelvis	7	4 / 2	11	5	4	1	3
	Ankle	19	5 / 3	24	11	1	1	0
	Elbow	3	1 / 1	4	3	1	0	1
	Femur	0	1	1	0	0	0	0
	Tibia	1	2 / 1	3	1	0	0	0
	Humerus	1	0	1	1	0	0	0
	Sacrum	3	0	3	2	0	0	0
Non major fractures	Carpus	3	0	3	3	0	0	0
	Clavicle	1	0	1	1	0	0	0
	Ribs	4	2	6	4	0	0	0
	Metatarsus	12	2 / 2	14	11	0	0	0
	Metacarpus	0	0	0	0	1	0	1
	Patella	2	0	2	2	0	0	0
	Scapula	1	0	1	0	0	0	0
	Tarsus	4	0	4	4	0	0	0
MOFs FRAX	%	67.6	54.1	65.3	59.7	84.8	87.5	83.3
All major	%	85.6	89.2	86.2	79.0	97.8	100	96.7
Mean time to first fracture	Days	956±591 [5-2269]	-	-	973±619 [5-2269]	803±419 [18-1594]	817±482 [18-1594]	795±391 [51-1438]

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619 Highlights

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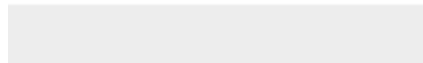
- 620 • 417 women of the FRISBEE cohort, matched for FRAX, were evaluated by HR-pQCT
- 621 • Some HR-pQCT parameters, mainly at radius, are discriminating for prevalent fractures
- 622 • HR-pQCT improves the risk prediction beyond the DXA but not the FRAX score
- 623 • UDR aBMD also provides valuable information



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**RDM Data Profile XML**

**BONE-D-20-00367\_DataProfile.xml**



## Authorship Statement

1. Conception or design of the work.

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2. Data collection.

Cappelle S.I, Kinnard V.

3. Data analysis and interpretation.

Cappelle S.I., Bergmann P., Moreau M., Body J.J.

4. Drafting the article.

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