Bone mineral content and areal density, but not bone area, predict incident fracture risk: a comparative study in a UK prospective cohort

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Abstract

Background—Low areal bone mineral density (aBMD), measured by dual-energy X-ray absorptiometry (DXA), is a well-established risk factor for future fracture, but little is known about the performance characteristics of other DXA measures such as bone area (BA) and bone mineral content (BMC) in fracture prediction. We therefore investigated the predictive value of BA, BMC and aBMD for incident fracture in a prospective cohort of UK women.

Methods—In this study, 674 women aged 20-80 years, recruited from four GP practices in Southampton, underwent DXA assessment (proximal femur, lumbar spine, total body) between 1991-1993. All women were contacted in 1998-1999 with a validated postal questionnaire to collect information on incident fractures and potential confounding factors including medication use. 443 women responded and all fractures were confirmed by assessment of images and radiology reports by a research nurse. Cox proportional hazards models were used to explore the risk of incident fracture and results are expressed as Hazard Ratio (HR) per 1 SD decrease in the predictor and 95% CI. Associations were adjusted for age, BMI, alcohol consumption, smoking, HRT, medications and history of fracture.

Results—55 women (12%) reported a fracture. In fully adjusted models femoral neck BMC and aBMD were similarly predictive of incident fracture. Femoral neck BMC: HR/SD=1.64 (95%CI: 1.19, 2.26; p=0.002); femoral neck aBMD: HR/SD=1.76 (95%CI: 1.19, 2.60; p=0.005)]. In

contrast femoral neck BA was not associated with incident fracture, HR/SD= 1.15 (95%CI: 0.88, 1.50; p=0.32). Similar results were found with bone indices at the lumbar spine and whole body.

Conclusions—In conclusion, BMC and aBMD appear to predict incident fracture with similar HR/SD, even after adjustment for body size. In contrast, BA only weakly predicted future fracture. These findings support the use of DXA aBMD in fracture risk assessment, but also suggest that factors which specifically influence BMC will have relevance to the risk of incident fracture.

Keywords

Introduction

Areal bone mineral density (here abbreviated as aBMD) measurement by DXA is the basis of the World Health Organization's 1994 operational definition of osteoporosis[1]. Many studies have consistently demonstrated the predictive value of aBMD for incident fracture, with an approximate doubling of fracture risk for each standard deviation decrease in aBMD, dependent on the site of measurement and the site of fracture[2]. In contrast, the value of other measurements derived from DXA such as bone area (BA) and bone mineral content (BMC) has not been commonly investigated[3]. DXA assessment of bone mineral is derived from pixel level attenuation of the x-ray beam, which is usually calibrated as a measure of aBMD[4]. Since every pixel has the same area, at this level, bone mineral content and areal bone mineral density are directly proportional (pixel BMC = pixel aBMD x pixel area). This relationship, and the number of pixels in the region of interest (e.g. femoral neck), permit calculation of total bone mineral content as the sum of individual pixel level BMC values (equivalent to the sum of pixel level aBMD values multiplied by the area of a pixel), whilst the mean aBMD across the region of interest is calculated as the sum of the individual pixel aBMD values divided by the number of pixels. Thus whilst, at the pixel level, aBMD and BMC are intimately related, at the level of a standard assessment site such as the femoral neck, they yield partly different information.

In this prospective cohort study, we therefore aimed to investigate the predictive value of bone area, mineral content and areal bone mineral density at the femoral neck, lumbar spine and whole-body sites for incident fracture.

Materials and Methods

Study population

Four general medical practices in different areas of Southampton, UK (inner city, suburban and rural) agreed to participate in the study, covering a broad social demographic. Recruitment for the baseline study took place between 1991 and 1993. Women were randomly selected from practice registers within seven 10-year age strata between 20 and 89 years with the aim of achieving 100 subjects per decade of age. Participants were then invited by letter, sent by their general practitioner (GP), to attend Southampton General Hospital for bone densitometry. Non-responders were encouraged to participate in the study on two further occasions before being excluded. Substitute subjects were then randomly

recruited in the age categories with subjects missing. Women who were pregnant at the time of recruitment were not scanned until after the birth of their child. The study was approved by the Southampton Joint Ethics Committee.

Baseline assessment

At the time of recruitment 1991-1993 a questionnaire was completed by an interviewer. Information recorded included age, height, weight, ethnic group, alcohol consumption, smoking, medical history, drug history and physical activity. Using the Lunar DPX+ densitometer (software version 3.4j, Lunar Corporation, Madison, Wisconsin, USA), with scanning and analysis protocols recommended by the manufacturer, measurements of the anteroposterior (AP) lumbar spine, right proximal femur and total body were obtained [bone area (BA), bone mineral content (BMC) and areal bone mineral density (BMD) except for whole body, at which site BA was not captured]. The densitometer was calibrated daily according to the manufacturer's standard procedure. A weekly further check was made using the manufacturer's aluminium spine phantom immersed in 15cm of water. The long-term precision (%CV) of the system over the duration of the study was 0.5%. All scans were examined by an experienced operator at the end of the study and technically unsatisfactory data were excluded from the database.

Follow-up assessments

A follow-up study commenced in 1998 on the 674 women for whom adequate baseline bone density measurements were available. Following renewed approval by the Southampton Joint Ethics Committee, postal questionnaires were sent out to the women who had originally attended a DXA assessment at baseline. A validated questionnaire was used to gather data on incident fractures which occurred during the 5-7 years between baseline DXA and follow-up. Participants were encouraged to return the questionnaire regardless of whether or not they had suffered a fracture. Participants listed fractures and dates of fractures in the period since their DXA scan and also in which hospital they were assessed. Data on medication use [hormone replacement therapy, bisphosphonates (etidronate and alendronate), calcium supplements and steroids] were collected. A senior research nurse, who checked radiographs and radiology reports, and classified the fracture site, undertook fracture validation. Vertebral fractures were classified as those with a definite clinical event with minimal trauma and at least a 20-25% reduction in anterior, middle or posterior height of any T4-L4 vertebra together with at least a 10-20% reduction of the projected vertebral area on visual inspection of a lateral radiograph.

Statistical analysis

To assess differences between groups, T-tests were used for normally distributed variables, Mann-Whitney U test for BMI (as the variable was not normally distributed) and Pearson Chi^2 test for categorical variables. Cox proportional hazards models were used to explore the time to first incident fracture and results were expressed as the Hazard Ratio (HR) per 1 SD increase in the predictor and 95% confidence interval. Outcomes included any 1) fracture; 2) the grouping of osteoporotic fractures (spine, hip, pelvis, distal radius/ ulna, clavicle, scapula, rib or humerus); and 3) the grouping of major osteoporotic fracture (spine, hip,

distal radius/ ulna or humerus). Covariates considered included age, BMI, alcohol consumption, smoking, HRT, medications and history of fracture.

Results

Participants

Original invitations to participate were sent out to 1157 women. 702 participants responded and attended for DXA assessment between 1991 and 1993. Of these individuals, nine participants were excluded on the basis of ethnicity, and two individuals in the 80-89 year age group could not be scanned due to physical frailty or dementia. Adequate scans could not be performed for technical reasons in a number of other cases leading to the elimination of 37 spine, 17 femur and 8 total body scans from the data set. Of the 674 women scanned between 1991 and 1993, a questionnaire on fracture incidence was returned by 443 participants (66% response rate).

Baseline characteristics at DXA visit of whole cohort and of those assessed at follow-up

The baseline characteristics (at 1991-1993 DXA visit) of the subset followed up in 1998-1999 were similar to those of the whole cohort originally assessed by DXA. Overall, 55 of the 443 participants assessed at follow-up in 1998-1999 reported at least one fracture, with four participants reporting two fractures. Compared with the entire cohort who had undergone DXA assessment (n=674), those who had experienced a fracture during follow-up were older (mean age 61.1 years versus 52.8 years, p<0.001) and a greater proportion had undergone hysterectomy (30.9% versus 16.7%, p=0.01). The fracture group had lower BMC at the femoral neck (p<0.001), lumbar spine (p<0.001) and whole body (p=0.003), in addition to a lower aBMD at all three sites (p<0.001). There were no differences between the bone area of the lumbar spine or femoral neck. Table 1 summarises these comparisons.

Incident fractures

The number of fractures by site is presented (n=55, first fractures only) in Figure 1. Fractures of the distal ulna or radius were the most frequently observed, representing 21.8% of fractures, followed by fractures of the ankle (14.5%) and metatarsals (10.9%). 26 fractures were classified as osteoporotic. There were two hip and two pelvic fractures, and one documented vertebral fracture.

DXA indices and risk of incident fracture

In fully adjusted models, the HR for any incident fracture per 1SD decrease in femoral neck BMC was 1.64 (95%CI: 1.19, 2.15), in comparison with 1.76 per 1SD decrease in femoral neck aBMD (95%CI: 1.19, 2.60), summarised in Table 2 and Figure 2a. Very similar effect sizes were observed for lumbar spine BMC (1.61; 95%CI: 1.15, 2.26) and aBMD (1.76; 95%CI: 1.25, 2.49). Whole body BMC and aBMD were also predictors of fracture, with the HR/SD for whole body BMC of 1.64 (95%CI: 1.10, 2.44) and aBMD of 1.74 (95%CI: 1.23, 2.47) after full adjustment for potential confounders. Neither femoral neck nor lumbar spine area was a statistically significant predictor of fracture risk. Similar relationships were observed for incident osteoporotic fracture (Table 3 and Figure 2b). Although the HR/SD point estimate for femoral neck aBMD (3.34; 95%CI: 1.82, 6.13) was greater than that for

femoral neck BMC (1.94; 95%CI: 1.22, 3.09), Figure 2b illustrates that the 95%CIs largely overlap. Finally, the associations were similarly observed with major osteoporotic fracture as the outcome, albeit of weaker statistical significance, reflecting the smaller number of outcomes (Online Supplementary Table 1).

Discussion

In this prospective study we demonstrated that, using DXA, both femoral neck and lumbar spine BMC and aBMD were similarly predictive of any incident fracture with HR/SD of 1.5-1.8, after adjustment for confounding factors. With osteoporotic fracture as the outcome, the HR/SD point estimate for BMD at the femoral neck was greater than that for BMC at that site, but the confidence intervals largely overlapped, and were consistent with there being no difference. Conversely, BA at the femoral neck or lumbar spine was not found to be a predictor of fracture risk.

Our results are strikingly similar to those reported by Cummings et al in 1994, which is the only prospective study of which we are aware to link measurement of BMC with fracture risk. Our data, showing that a 1SD decrease in BMC at the femoral neck was associated with a 1.94-times increased risk of fragility fracture, and that a 1SD decrease in aBMD at the femoral neck was associated with a hazard ratio of 3.34 for fragility fracture in fully adjusted models, are consistent with this previous study. Cummings et al reported that each SD decrease in femoral neck BMC was associated with a 1.6-times (95%CI: 1.3, 2.1) increase in hip fracture risk, whilst each SD decrease in femoral neck aBMD was associated with a 2.6-times (95%CI: 2.0, 3.5) hip fracture risk. In the present study, although the point estimate for the HR/SD for aBMD was greater than that for BMC at the femoral neck in the prediction of fragility fractures, the 95% confidence intervals overlapped to the extent that similarity remains possible; the effect sizes at the femoral neck were rather similar when using all incident fractures as the outcome (1.76 vs 1.64 respectively). An analogous pattern of similarity between HR/SD for aBMD and BMC predicting all fractures was observed at both lumbar spine and whole body sites (ranging from 1.61 to 1.76), and with the marginally greater magnitude of the HR/SD for aBMD than BMC much less marked for these sites with fragility fracture as the outcome, and again largely overlapping confidence intervals regardless of fracture outcome studied. Overall, although both total BMC and aBMD have predictive value, our findings support the international consensus that aBMD at the femoral neck is the preferred reference standard site for osteoporosis risk stratification[5–8]. However, they also support the notion that associations with BMC, such as those documented between early growth and adult bone mass, are likely to have clinical relevance[9,10]. It is interesting that the predictive value of BA was substantially less than that of BMC or aBMD, given that BMC partially depends on bone size. Importantly, DXA BA has contributions from bone width and length, but in reality mineral is distributed over length, breadth and depth. Indeed studies using QCT have demonstrated that cortical cross-sectional area at the femoral neck is lower in hip fracture patients than in non-fracture controls[11], and that tibial and radial cross-sectional area are predictive of incident fracture[12]. Importantly with pQCT the measure of cross sectional area includes no contribution from bone length. In contrast bone area measured by DXA depends on both width and length, attributes with likely opposing influences on fracture risk, since greater

height leads to greater impact force in a fall. Such local geometric considerations, coupled with the skeleton's adaption of size and shape to the increased loads imposed on it by a larger body size[13], may underlie the lack of observed associations between BA and incident fracture.

We studied a well-characterised cohort with validated fracture ascertainment, but there are several limitations that should be considered in the interpretation of our findings. Firstly, the age distribution of our population was rather older than that of the UK population as a whole, and selection bias towards a higher fracture risk cannot be excluded, reducing the potential generalizability of our findings. Secondly, we were not able to definitively classify fractures as low or high trauma, as we lacked information on fracture causation; instead we used the fracture site to infer fragility, an approach which is well-established in older adults[14]. Thirdly, we obtained information on comorbidities directly from participants, which may have led to inaccuracies compared with physician reporting. Overall this is likely to have simply reduced the precision of our results. Fourthly, our measures of bone area are projectional and so are not necessarily representative of bone strength in physiological cross-section. Finally the DXA scanner used in the study was not able to assess whole body bone area, so this measure could not be included in the analysis.

In conclusion, we have demonstrated, in a prospective cohort, that both BMC and BMD, but not BA, at the hip, lumbar spine and whole-body sites are predictive of incident fracture. Although the magnitude of predictive value for fragility fracture was greater for femoral neck BMD than BMC (albeit with partly overlapping confidence intervals), at all other sites the point estimates appeared similar between BMC and BMD. These findings support the international consensus on the use of femoral neck BMD as the reference measure for osteoporosis risk assessment, and additionally the clinical relevance of BMC-specific associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Summary

We studied a prospective UK cohort of women aged 20 to 80 years, assessed by DXA at baseline. BMC and aBMD, but not BA, at femoral neck, lumbar spine and whole body sites were similarly predictive of incident fractures.
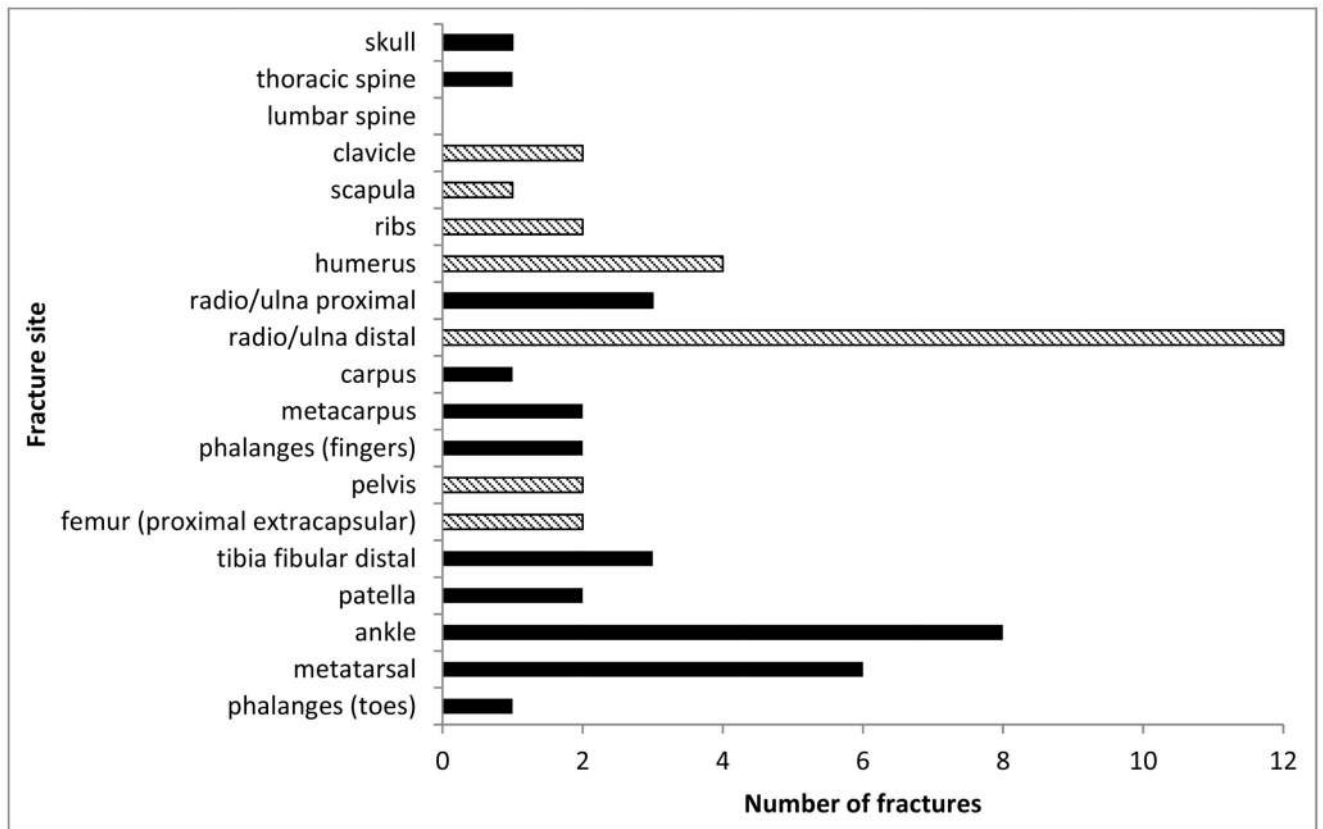
Figure 1.
Fractures by site (n=55). Osteoporotic (fragility) fractures are shown in patterned bars
(n=26), other fractures in solid bars.
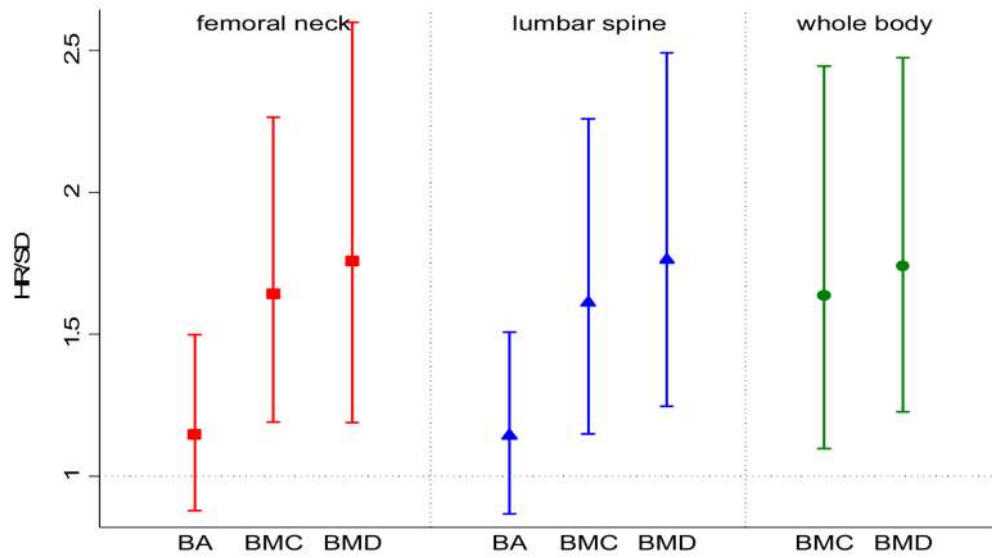
a) any fracture

b) osteoporotic fracture

Figure 2.
HR/SD for BA, BMC and BMD at femoral neck for a) any incident fracture and b) incident osteoporotic fracture.

Table 1

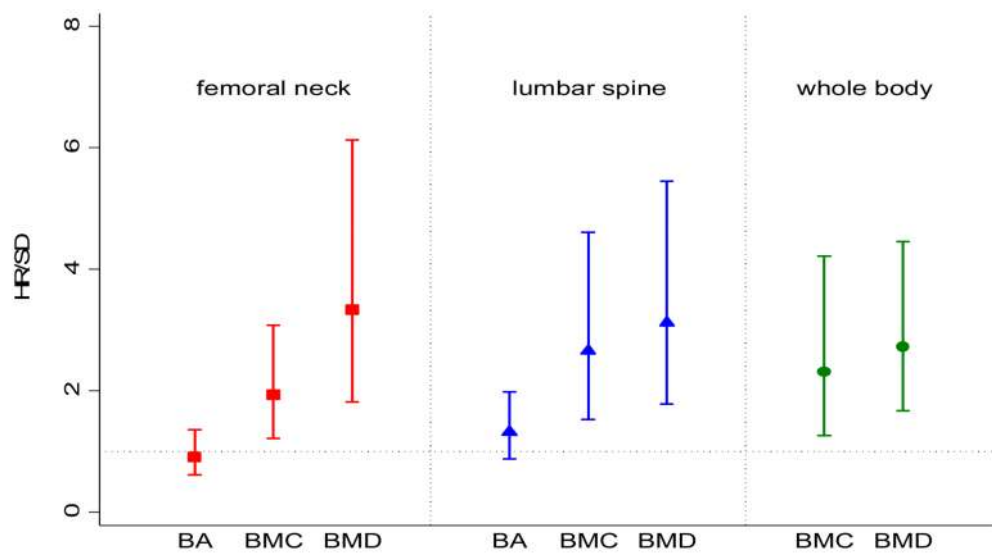Baseline characteristics of the population at DXA assessment.

Characteristics	All (n=674)	All followed-up (n=443)	p[a]	Reported fracture during follow-up (n=55)	p[b]
Age at scan: mean (SD)	52.5 (17.6)	52.8 (16.1)	0.79	61.1 (15.2)	<0.001
Height (cm): mean (SD)	160 (6.9)	160.3 (6.7)	0.44	158.9 (6.1)	0.24
Weight (kg): mean (SD)	66.0 (12.6)	67.1 (12.6)	0.19	66.8 (12.0)	0.65
BMI: median (IQR)	24.9 (22.4-28.5)	25.1 (22.6-28.8)	0.26	25.8 (23.2-28.7)	0.18
Ever pregnant: N (%)	509 (75.5)	346 (78.1)	0.32	43 (78.2)	0.66
Hysterectomy: N (%)	109 (16.2)	74 (16.7)	0.81	17 (30.9)	0.005
Pill >5 years: N (%)	158 (23.4)	111 (25.1)	0.65	4 (7.3)	0.008
Bone characteristics					
Area (cm^2): mean (SD)					
Femoral neck	4.76 (0.49)	4.76 (0.49)	0.94	4.78 (0.52)	0.77
Lumbar spine	53.78 (5.18)	54.07 (5.19)	0.37	53.33 (4.87)	0.55
BMC (g): mean (SD)					
Femoral neck	4.38 (0.88)	4.45 (0.87)	0.2	3.99 (0.73)	0.002
Lumbar spine	61.60 (13.79)	62.50 (13.74)	0.3	55.28 (12.87)	0.001
Whole body	2540.0 (476.7)	2581.8 (471.1)	0.15	2376.6 (528.2)	0.02
BMD (g/cm^2): mean (SD)					
Femoral neck	0.92 (0.16)	0.93 (0.16)	0.15	0.84 (0.16)	<0.001
Lumbar spine	1.14 (0.19)	1.15 (0.19)	0.34	1.03 (0.19)	<0.001
Whole body	1.13 (0.11)	1.14 (0.11)	0.15	1.08 (0.13)	0.001

[a] p-value for comparison of baseline participant characteristics at DXA assessment between full cohort and subset who underwent follow-up

[a] p-value for comparison of baseline participant characteristics at DXA assessment between full cohort and subset who reported a fracture during the follow-up. (T-test for normally distributed variables, Mann-Whitney test for BMI (not normally distributed), Chi^2 test used for categorical variables).

Table 2

Hazard ratio per 1 SD decrease in predictor) for DXA indices (femoral neck, lumbar spine and whole body BMC, BMD and area) and any incident fracture.

Predictor	Unadjusted			Adjusted for age			Fully adjusted HR/SD[‡]		
	HR/SD[†]	95%CI	p-value	HR/SD[†]	95%CI	p-value	HR/SD[†]	95%CI	p-value
Femoral neck									
Area	0.99	0.76, 1.29	0.93	1.1	0.85, 1.42	0.47	1.15	0.88, 1.50	0.32
BMC	1.82	1.38, 2.41	<0.001	1.58	1.16, 2.15	0.004	1.64	1.19, 2.26	0.002
BMD	2.04	1.51, 2.77	<0.001	1.72	1.18, 2.51	0.005	1.76	1.19, 2.60	0.005
Lumbar spine									
Area	1.19	0.90, 1.57	0.22	1.1	0.84, 1.44	0.49	1.14	0.87, 1.51	0.35
BMC	1.85	1.38, 2.49	<0.001	1.53	1.11, 2.11	0.01	1.61	1.15, 2.26	0.006
BMD	1.97	1.49, 2.60	<0.001	1.67	1.21, 2.31	0.002	1.76	1.25, 2.49	0.001
Whole body									
BMC	1.71	1.27, 2.31	<0.001	1.4	1.01, 1.94	0.04	1.64	1.10, 2.44	0.02
BMD	1.79	1.40, 2.29	<0.001	1.53	1.13, 2.06	0.006	1.74	1.23, 2.47	0.002

[†] HR for any fracture per 1 SD decrease in the predictor

[‡] Adjusted for age, BMI, alcohol, smoking, HRT, previous fractures, medication

Table 3

Gradient of risk (hazard ratio per 1 SD decrease in predictor) for DXA indices (femoral neck, lumbar spine and whole body BMC, BMD and area) and incident osteoporotic fracture.

Predictor	Unadjusted			Adjusted for age			Fully adjusted GR[‡]		
	HR/SD[†]	95%CI	p-value	HR/SD[†]	95%CI	p-value	HR/SD[††]	95%CI	p-value
Femoral neck									
Area	0.77	0.51, 1.17	0.223	0.9	0.60, 1.34	0.59	0.92	0.61, 1.36	0.67
BMC	2.2	1.47, 3.28	<0.001	1.9	1.21, 2.99	0.006	1.94	1.22, 3.09	0.005
BMD	3.32	2.05, 5.38	<0.001	3.16	1.76, 5.66	<0.001	3.34	1.82, 6.13	<0.001
Lumbar spine									
Area	1.44	0.96, 2.16	0.08	1.29	0.87, 1.90	0.2	1.32	0.88, 1.99	0.18
BMC	2.97	1.87, 4.71	<0.001	2.52	1.49, 4.26	0.001	2.66	1.53, 4.61	0.001
BMD	3.09	2.02, 4.72	<0.001	2.9	1.72, 4.89	<0.001	3.12	1.79, 5.45	<0.001
Whole body									
BMC	2.44	1.54, 3.87	<0.001	2	1.20, 3.33	0.008	2.31	1.27, 4.22	0.006
BMD	2.53	1.79, 3.57	<0.001	2.35	1.54, 3.61	<0.001	2.73	1.67, 4.46	<0.001

[†]HR for osteoporotic fracture per 1 SD decrease in the predictor

[‡]Adjusted for age, BMI, alcohol, smoking, HRT, previous fractures, medication