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High osteoporotic fracture risk and CVD risk co-exist in postmenopausal women ☆

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ABSTRACT

Introduction: Osteoporosis related risk factors such as BMD have been associated with cardiovascular endpoints in previous studies but there have been no studies of integrated risk using risk factor algorithms.
Methods: A sample of 358 peri- and postmenopausal women, mean age 59.3 (range 45–74) years were studied. Each individual had bone mineral density (BMD) measurements by dual energy X-ray absorptiometry. Fracture risk was assessed using the WHO FRAX algorithm and cardiovascular disease (CVD) risk using the Framingham Risk Tool.
Results: Women with higher 10 year risk of major osteoporotic had significantly higher cardiovascular risk (4.634% vs 8.36%, p = 0.001). In multiple regression analysis, 5-year CVD risk was significantly associated with the 10-year risk of having major osteoporotic (β = 0.095, p = 0.001) and hip (β = 0.055, p = 0.001) fracture. Women with the highest CVD risk were 5.4 times more likely to have higher risk of major osteoporotic fracture.
Conclusions: Fracture risk, determined by using a multiple risk factor algorithm such as FRAX, was positively associated with higher cardiovascular risk determined by using the Framingham Risk Tool. Awareness regarding these concurrent risk factors needs to be raised so that appropriate risk reduction can be implemented.

Introduction

The existence of a possible link between bone and atherogenic pathways has been recognized for some time. Inverse relationships between bone mineral density (BMD) and calcified atherosclerotic plaque have been reported in a number of population-based studies of postmenopausal women [1–5]. A number of studies have also focused on the relationship between plasma lipids and BMD [6–8].

Although BMD has shown a strong association with fracture risk, most fractures occur in subjects with *T*-scores above −2.5, the threshold typically used to define osteoporosis, which means that relying solely on BMD will miss many patients at risk of fracture. Clinical risk factors are also associated with an increased probability of osteoporosis-associated fractures in postmenopausal women, and a number of algorithms have integrated multiple clinical risk factors, with or without BMD, to produce estimates of absolute risk of osteoporotic fracture.

This approach of integrating multiple clinical risk factors which may be additive or synergistic has been well developed in the cardiovascular field with a number of tools for estimating absolute risk of cardiovascular disease (CVD) in clinical practice with good predictive ability [9–14].

In the present study, we investigated the relationship between bone and cardiovascular pathways by calculating fracture risk using the FRAX [15–18] tool and comparing it to cardiovascular risk assessed by the Framingham Heart Risk tool [9,10] in a large population of peri and postmenopausal women.

Methods

Subjects

Study subjects were female twins over 45 years, recruited as part of the Northern Sydney Twin Study. Information from this twin cohort has been published in detail previously [7,19–22]. In brief, the twins were recruited through the Australian National Health and Medical Research Council (NHMRC) Twin Registry and from local media campaigns. Twins were invited to participate in an investigation into the genetic and environmental determinants of various diseases including osteoarthritis, cardiovascular disease, asthma, and osteoporosis. The hospital's Human Research Ethics Committee approved the study. After providing written informed consent, each twin was interviewed separately in accordance with a standard questionnaire to collect demographic, lifestyle and medical history data.

Except for hormone therapy, twins who used medications or who had medical conditions that could interfere with bone metabolism were excluded from the analysis. Hormone therapy use was recorded and included as a covariate in the statistical analyses. Menopause,

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either natural or surgical, was defined as self-reported 12-month amenorrhoea [23] and years since menopause (YSM) were recorded. No blood hormone levels were investigated. Incidents of myocardial infarctions (MI), heart failure and stroke were documented.

Zygosity in same-sex twins was determined from the twins' self-report using questions from a validated questionnaire [24]. DNA fingerprinting was used to determine zygosity in twin pairs in which their zygosity was either unknown or disputed.

Clinical characteristics and laboratory measurements

Characteristics of study participants included age, height (m), weight (kg), BMI (kg/m^2), systolic and diastolic blood pressure, menopausal status, hormone therapy and OCP use, physical activity, alcohol intake and smoking history, prior low-trauma fracture history as an adult, history of parental hip fracture, use of glucocorticoids, diagnosis of rheumatoid arthritis and secondary osteoporosis.

Fasting blood samples used in this study were collected and kept as aliquots at −80 °C until analysis. Fasting serum total cholesterol (TC), high density lipoprotein (HDL), and triglycerides (TG) were measured and low density lipoprotein (LDL) levels were calculated using standard formula: LDL = TC − HDL − (TG/5). Aortic calcification was assessed from lateral thoracolumbar X-rays as described by Kauppila et al. [25].

Bone mineral density measurements

Lumbar spine (LS), total hip, forearm and whole body scans were performed on a fan beam dual-energy X-ray absorptiometry (DEXA) bone densitometer (QDR 4500W, Hologic, Waltham, MA USA) at baseline and follow-up visits. Measurements of bone mineral density (BMD) of lumbar spine (LSMBD), femoral neck (FNBMD), total hip (HTBMD), forearm (FORBMD) and whole body (WBBMD) were obtained using standard protocols as previously described [7,19–21]. The same densitometer was used throughout the entire study. Performance of the DEXA scanner has been monitored. Routine daily QC scans of the Spine Phantom were performed and the coefficient of variation for QC BMD measures in our unit was 0.98%. In vivo reproducibility has been estimated from duplicate scans (155 patients with repositioning between scans) as coefficients of variation (CV) and intraclass correlation (ICC) for BMD measures. CV and ICC for LS, total hip, femoral neck BMD were 0.74/0.998; 1.23/0.994 and 1.27/0.994 correspondingly.

The FRAX tool and fracture risk

FRAX® is a risk-assessment tool [15–18] developed from population-based cohorts in Europe, North America, Asia, and Australia that calculates the 10-year probability of hip fracture and major osteoporosis-related fracture (clinical spine, forearm, hip, or proximal humerus). FRAX comprises 11 clinical variables (age, sex, weight and height [to give body mass index (BMI)], previous fracture as an adult, parental hip fracture, current cigarette smoking, current (or 3 months of past) use of glucocorticoids, diagnosis of rheumatoid arthritis, consumption of three or more units of alcohol daily, and secondary osteoporosis) as well as BMD-derived *T*-scores at the femoral neck. The 10-year probability risk of major osteoporotic (OSFrR) or hip fracture (HipFrR) was determined using the FRAX® risk-assessment tool developed from Australian population-based cohort. The FRAX® risk-assessment tool was used with and without BMD.

Absolute cardiovascular disease risk assessment

The Framingham Risk Equation is a predictive equation derived from the Framingham Heart Study, which started in 1948 and has been operational for more than 60 years. It was developed for several cardiovascular disease endpoints by Anderson and colleagues in 1991 [9,10]. The Framingham Risk Equation demonstrates predictive ability that is equal or superior to other methods of calculating absolute CVD risk, and is therefore recommended for use in Australian primary care. It has been incorporated into the online Australian absolute cardiovascular disease risk calculator that has been used in this study cohort to predict the risk of a cardiovascular event over the next 5 years [9,10,26]. The calculator is designed for use in adults aged 45–74 years without existing CVD or not already known to be at increased risk of CVD, the latter defined as the following groups — diabetes and age > 60 years; diabetes with microalbuminuria; moderate or severe chronic kidney disease; previous diagnosis of familial hypercholesterolaemia; systolic blood pressure ≥ 180 mm Hg or diastolic blood pressure ≥ 110 mm Hg; serum total cholesterol > 7.5 mmol/L).

Statistical methods

All statistical analyses were performed using the IBM SPSS Statistics v19 (SPSS Inc., Chicago, IL). For comparison between groups of 10-year risk of having major osteoporotic fracture tertiles, ANOVA analysis for continuous variables and chi-square tests for categorical variables were performed. To study the association between 10-year risk of having major osteoporotic or hip fracture and 5-year CVD risk, multiple regression analysis was performed. All risk scores were log-transformed for the analysis. Since both FRAX and the Framingham Risk Tool incorporate age and BMI as risk factors, those were not added in multiple regression analyses. Regression models were adjusted for years since menopause (YSM) and HRT use. Results from crude and adjusted models were obtained. FRAX options with and without BMD were used to calculate 10-year major osteoporotic and hip fracture risks. These were log transformed and used as dependent variables in each regression model. Log 5-year CVD risk was entered into crude and adjusted models as an independent continuous variable to calculate regression coefficients. Adjusted means for log 10-year major osteoporotic and hip fracture (with and without BMD) were obtained from fully fitted regression models where 5-year CVD risk was entered as the independent factor (categorised). Other possible confounders include Menopausal status, HRT use and physical activity, and these were accounted for in the regression models. Adjusted means for total aortic calcification (dependent) were derived from regression models where categories of 10-year OSFrR tertiles were entered as independent factors and YSM, HRT use and physical activity as covariates.

Results

We studied 480 healthy twin volunteers (230 pairs) in 2010 (96 monozygotic (MZ) and 134 dizygotic (DZ) pairs). For this study we randomly excluded one member of each MZ twin pair (n = 96) and subjects who were not suitable for calculating absolute CVD risk, such as individuals over 74 years of age (n = 6). There were 7 incidences of MI, 5 — heart failure, 8 — stroke reported in this study cohort. These subjects were also excluded.

There were 358 women with a mean age of 59.3 (range 45–74) included in this analysis.

Main characteristics of the participants stratified by 10-year OSFrR tertiles are presented in Table 1.

Estimations of 10-year probability risk of having major osteoporotic or hip fracture were slightly higher using the FRAX tool without BMD included in the equation.

As expected, women in the highest tertile of FRAX 10-year OSFrR were older and had significantly lower BMD measures at all skeletal sites.

These women also had higher total aortic calcification score (4.41 ± 4.86 compared to 2.18 ± 3.57 in the lowest tertile).

As the cohort of this study was relatively young and healthy volunteers, the average 10-year probability risks of major osteoporotic or hip

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Table 1
Characteristics of the study cohort stratified by tertiles of FRAX assessed 10-year probability risk of having major osteoporotic fracture (with BMD). Data are mean ± SD, unless specified otherwise.

	Tertiles of FRAX assessed 10-year probability risk of having major osteoporotic fracture (with BMD)				P
	Total (N = 358)	1 N = 119	2 N = 120	3 N = 119	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
10-year major OS Fr risk (with BMD)	4.17 ± 3.49	1.45 ± 0.42	3.14 ± 0.67	7.99 ± 3.69	0.000
10-year major OS Fr risk (without BMD)	5.42 ± 4.77	1.84 ± 0.75	4.04 ± 1.51	9.98 ± 5.45	0.000
10-year hip Fr risk (with BMD)	0.92 ± 1.70	0.11 ± 0.11	0.39 ± 0.27	2.3 ± 2.43	0.000
10-year hip Fr risk (without BMD)	1.77 ± 1.67	0.29 ± 0.23	0.96 ± 0.59	3.90 ± 4.13	0.000
Age (years)	60.56 ± 7.89	53.93 ± 5.33	60.58 ± 4.89	67.17 ± 7.06	0.000
BMI (kg/m^2)	26.87 ± 4.91	27.01 ± 5.15	27.37 ± 4.74	26.17 ± 4.79	0.148
Bone mineral density (g/cm^2)					
Lumbar spine	0.951 ± 0.158	1.028 ± 0.157	0.954 ± 0.146	0.871 ± 0.131	0.000
Femoral neck	0.751 ± 0.120	0.825 ± 0.121	0.754 ± 0.094	0.672 ± 0.092	0.000
Hip total	0.896 ± 0.125	0.971 ± 0.119	0.896 ± 0.107	0.823 ± 0.101	0.000
Forearm total	0.522 ± 0.057	0.557 ± 0.044	0.525 ± 0.049	0.484 ± 0.054	0.000
Whole body total	1.088 ± 0.116	1.158 ± 0.114	1.082 ± 0.092	1.023 ± 0.100	0.000
Aortic calcification score	3.20 ± 4.21	2.18 ± 3.57	2.03 ± 3.02	4.41 ± 4.86	0.032
Total cholesterol (mmol/L)	5.44 ± 0.98	5.57 ± 0.91	5.45 ± 0.94	5.30 ± 1.06	0.297
HDLC (mmol/L)	1.45 ± 0.39	1.49 ± 0.36	1.42 ± 0.39	1.43 ± 0.41	0.734
5-year CVD risk	6.68 ± 8.42	4.64 ± 7.23	7.03 ± 9.24	8.36 ± 8.25	0.000
5-year CVD risk (N (%))					0.000
<5%	191 (53.3%)	88 (73.9%)	65 (54.2%)	38 (31.9%)	
5–14.99%	115 (32.1%)	21 (17.6%)	41 (34.2%)	53 (44.5%)	
≥15%	52 (14.5%)	10 (8.4%)	14 (11.7%)	28 (23.5)	
Any fractures	72 (20.1%)	5 (4.2%)	27 (22.5%)	40 (33.6%)	0.000
Lifestyle characteristics					
Smoking history (N (%))					0.942
Never	224 (62.6%)	75 (63.0%)	72 (60.0%)	77 (64.7%)	
Current	42 (11.7%)	15 (12.6%)	15 (12.5%)	12 (10.1%)	
Ex-smoker	92 (25.7%)	29 (24.4%)	33 (27.5%)	30 (25.2%)	
Alcohol intake (N (%))					0.221
≤1 drink per week	143 (39.9%)	40 (33.6%)	49 (40.8%)	54 (45.4%)	
2–14 drinks per week	208 (58.1%)	77 (64.7%)	69 (57.5%)	62 (52.1%)	
≥14 drinks per week	7 (1.9%)	2 (1.6%)	2 (1.7%)	3 (2.5%)	
Physical activity (N (%))					0.811
None	19 (5.4%)	6 (5.0%)	8 (4.2%)	5 (4.2%)	
<30 min per day	165 (46.1%)	55 (46.2%)	51 (42.5%)	59 (49.6%)	
≥30 min per day	174 (48.6%)	58 (48.3%)	61 (50.8%)	55 (46.2%)	

fracture were relatively low at 4.17% (0.7–24) and 0.92% (0–15), respectively and mean 5-year CVD risk was also modest at 6.68% (0–38). Based on the Australian CVD risk guidelines, we categorised the 5-year CVD risk as very low (<5%, n = 191), low (5–9.9%, n = 115) and moderate to high (>10% n = 52) [27]. Moderate (10–14.9%, n = 26) and high (>15, N = 26) CVD risk groups were combined due to small numbers of individuals in these two groups. The prevalence of women with >10% 5-year CVD risk was higher in the highest tertile of 10-year probability of OSFrR.

There were 72 self-reported incidents of low-trauma fracture, with 40 (33.6%) of these fractures present in the highest tertile of 10-year OSFrR women.

There was a significant correlation between FRAX assessed 10-year probability risk of having major osteoporotic or hip fracture (with or without BMD) and 5-year CVD risk. Coefficients of nonparametric Spearman correlations are presented in Table 2.

Parameter estimates of the multiple regression models are presented in Table 3. We found that 5-year CVD risk was significantly associated with the 10-year risk of having major osteoporotic ($\beta = 0.150$, $p = 0.001$) and hip ($\beta = 0.076$, $p = 0.001$) fracture. These results were similar when 10-year OSFrR and HipFrR were estimated by FRAX no BMD option. After adjustment for other possible confounders including YSM; HRT use and physical activity, the association remained statistically significant.

Adjusted means of 10-year probability of OSFrR and HipFrR across categories of 5-year CVD risk are presented in Fig. 1. After adjustment for YSM, BMI, history of smoking, alcohol intake, HRT use and physical activity, mean 10-year risks of having a hip fracture were 0.49 ± 0.14; 1.04 ± 0.18 and 1.23 ± 0.25 across <5%, 5–10% and ≥10% categories of 5-year CVD risk, respectively ($p < 0.05$). Adjusted means of log10-year risks of having major osteoporotic fracture were 2.88 ± 0.27; 4.48 ± 0.35 and 4.42 ± 0.49 across categories of 5-year CVD risk, respectively ($p < 0.05$).

Adjusted means of total scores of aortic calcifications across tertiles of 10-year OSFrR are presented in Fig. 2 (models adjusted for YSM, HRT use and physical activity). Women in the highest tertile of 10-year OSFrR had significantly higher scores of aortic calcification compared to the women in lower tertiles (ACa scores: 4.6 vs 2.1 and 2.4 from high to low tertile of 10-year OSFrR, respectively, $p < 0.001$).

Odds Ratios (OR) and relative risk (RR) for prevalent higher 10-year probability risk of having major osteoporotic or hip fracture per higher

Table 2
Nonparametric Spearman correlations between 5-year CVD risk and FRAX assessed 10-year probability risk of having major osteoporotic or hip fracture (with or without BMD).

10-year major osteoporotic fracture risk	With BMD	0.427***
	Without BMD	0.418***
10-year hip fracture risk	With BMD	0.398***
	Without BMD	0.440***

*** $p < 0.001$.

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t3.1 **Table 3**
t3.2 Regression coefficients of the association between 5-year CVD risk and FRAX assessed
t3.3 10-year probability risk of having major osteoporotic or hip fracture (with or without
t3.4 BMD).

		Regression models	
		Model I (crude)	Model 2* (adjusted)
10-year major osteoporotic fracture risk	With BMD	0.150***	0.095**
	Without BMD	0.165***	0.101**
10-year hip fracture risk	With BMD	0.076***	0.055**
	Without BMD	0.099**	0.064*

t3.11 Dependent: log transformed10-year probability risk of having major osteoporotic or
t3.12 hip fracture with and without BMD. Independent: Log 5-year CVD risk.
t3.13 Model 1: not adjusted.
t3.14 Model 2: adjusted for YSM; HRT use and physical activity.
t3.15 *** p<0.001.
t3.16 ** p<0.01.
t3.17 * p<0.05.

Q3 247 5-year CVD are presented in Table 4. Women with the highest CVD risk
248 were 5.4 (95% CI 2.1–13.5) times more likely to have higher risk of
249 major osteoporotic fracture and 3.0 (95%CI 1.4–6.4) times more likely
250 to have higher hip fracture risk than women with lower CVD risk
251 (p<0.001).

Discussion

252

A number of previous studies have examined the relationship between bone and cardiovascular risk, mostly using single endpoints such as BMD and vascular calcification at various sites as reviewed by Anagnostis et al. [28]. BMD has been linked to aortic calcification and mortality from cardiovascular disease in these studies. We have previously reported that increased FRAX scores were associated with cardiovascular disease in a population of women in primary care [29]; however cardiovascular disease cases were self-reported in that study. The present study appears to be the first study to examine the association between integrated fracture risk and an integrated cardiovascular risk determined from multiple risk factors. We found that women with high fracture risk higher cardiovascular risk. Aortic calcification score was associated with 10-year OSFrR independently from YSM, HRT use and physical activity. Although both cardiovascular risk and fracture risk are age-dependent, this relationship was not explained by age alone.

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Our observation that fracture risk was positively associated with cardiovascular risk in the multiple regression analysis concurs with previous studies of single risk factors such as BMD or aortic calcification [28]. More recently Wang et al. [5] reported that BMD in the femur and total body but not the lumbar spine were decreased significantly in women with abdominal aortic calcification, however after

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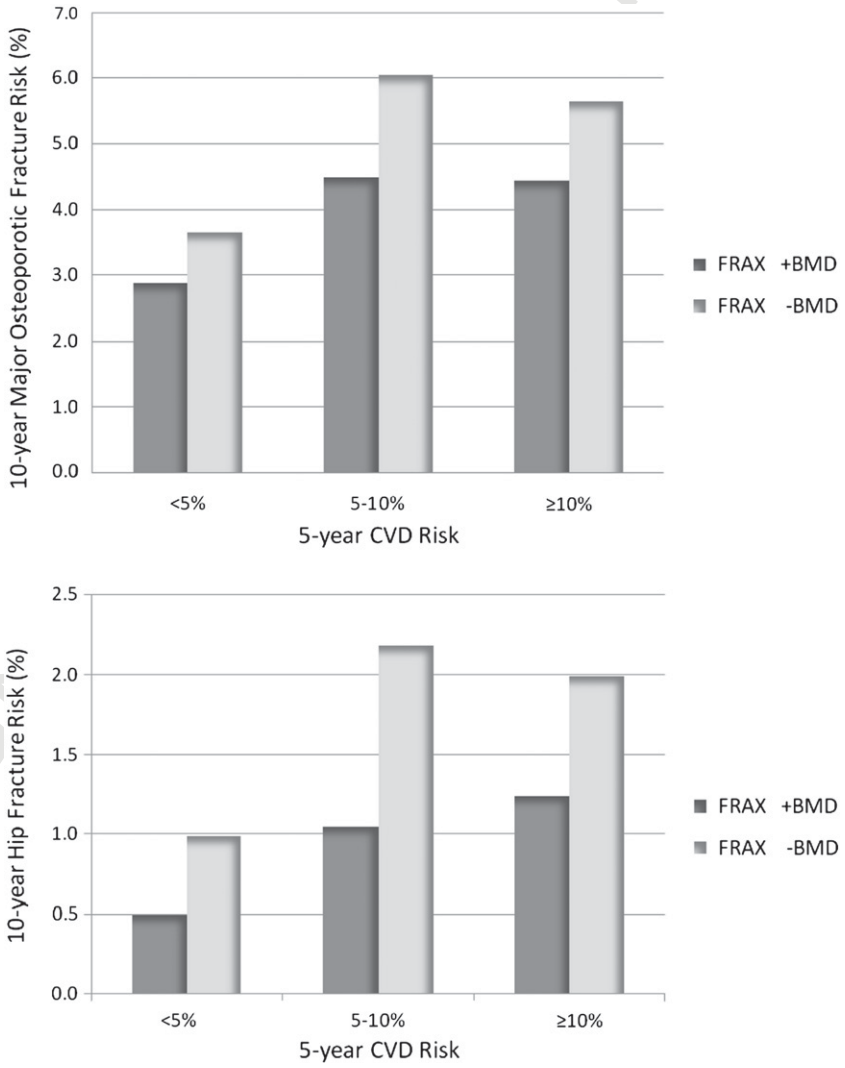

Fig. 1. Adjusted means* of FRAX 10-year probability risk of having hip or major osteoporotic fracture (with and without BMD) across categories of 5-year CVD risk. * Means adjusted for menopausal status, HRT use and physical activity.

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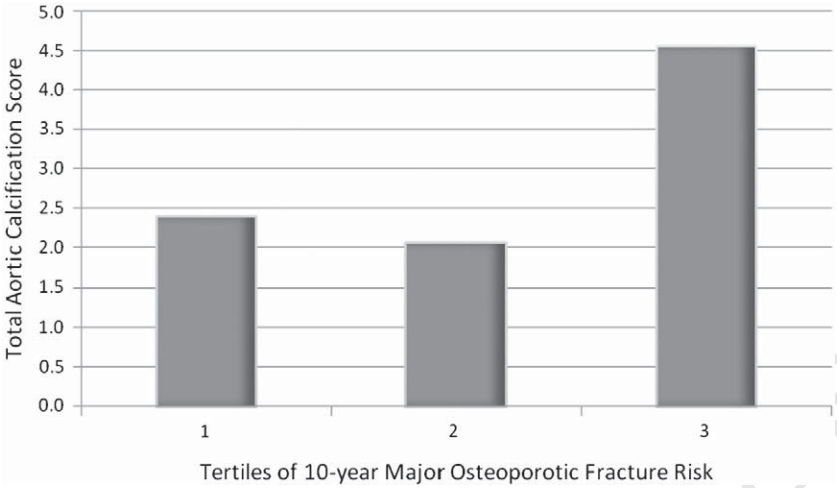

Fig. 2. Adjusted means* of total aortic calcification score across categories of 5-year CVD risk. * Means adjusted for YSM, HRT use and physical activity.

adjustment for age, aortic calcification was not related to BMD at any site. Divers et al. [30] recently examined the relationship between calcified atherosclerotic plaque and BMD in African-Americans. They observed significant inverse relationships between BMD and calcified plaque independent of conventional cardiovascular risk factors. However their population all suffered from type II diabetes unlike our healthy cohort. A number of studies have linked vascular calcification to fracture risk, mainly hip fractures, [31–35], but integrated fracture risk was not assessed in these studies.

A number of studies have also focused on the relationship between plasma lipids and BMD. Early postmenopausal women with an atherogenic lipid profile have been reported to have lower lumbar and femoral neck BMD and had an increased risk of osteopaenia than those with a normal lipid profile [6], suggesting that hyperlipidaemia may be associated with osteoporosis. An inverse relationship has been found between lumbar spine BMD and total cholesterol in postmenopausal women and HDL cholesterol in premenopausal women [7]. In a longitudinal study in postmenopausal women aged 50–75 years, those with the largest increases in serum cholesterol showed the greatest decreases in spine BMD independently of change in the body mass index [8]. More recently Buizert et al. reported no association between total cholesterol and broadband ultrasound attenuation in the calcaneus but higher levels of HDL cholesterol were associated with lower broadband ultrasound attenuation in the calcaneus [36] suggesting HDL cholesterol levels do not explain the association between osteoporosis assessed by QUS and CVD.

Our study has some strengths and limitations. Our population were healthy volunteers who had not previously been assessed for dual cardiovascular and fracture risk. However the healthy nature of our study cohort meant that incident fractures and cardiovascular events were very low and there was insufficient power to analyse these events as separate outcomes. Both cardiovascular risk and fracture risk include age in their equations. The resulting limitations to statistical analyses could not be entirely overcome.

In conclusion we found that fracture risk, determined using a multiple risk factor algorithm such as FRAX, was positively associated with higher cardiovascular risk, determined using the Framingham Risk assessment tool. The relationship between bone health and cardiovascular risk factors needs further investigation. Awareness regarding these concurrent risk factors needs to be raised so that appropriate risk reduction for modifiable factors can be instituted.

Table 4
Odds Ratios (OR) and relative risk (RR) for prevalent higher 10-year probability risk of having major osteoporotic or hip fracture per higher 5-year CVD risk (tertiles 1 as the lowest and 3 as the highest).

	OR	95% CI	p	RR	95% CI	p
Odds Ratio for OS_FrR (1/3)	5.36	2.13–13.48	0.000	3.07	1.46–6.43	0.000
Odds Ratio for Hip_FrR (1/3)	3.01	1.41–6.42	0.000	1.88	1.13–3.14	0.000

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