Low BMD is Less Predictive Than Reported Falls for Future Limb Fractures in Women Across Europe: Results From The European Prospective Osteoporosis Study (EPOS)

Kaptoge S.[1], Benevolenskaya L. I.[3], Bhalla A. K.[4], Cannata J. B.[5], Boonen, S[7], Falch J. A.[8], Felsenberg D.[9], Finn J. D.[2], Nuti R.[10], Hoszowski K.[11], Lorenc R.[15], Lyritis G.[16], Masaryk P.[17], Naves-Diaz M.[5], Poor G.[19], Reid D. M.[20], Scheidt-Nave C.[21], Stepan J.J.[22], Todd C J.[23], Weber K.[24], Woolf A. D.[25], Roy D. K.[2], Lunt M.[2], Pye S. R.[2], O'Neill T. W.[2], Silman A.J.[**2], Reeve J.[** 1].

[1] *Strangeways Research Laboratory, University of Cambridge, Cambridge, UK*
[2] *ARC Epidemiology Unit, University of Manchester, Manchester, UK*
[3] *Institute of Rheumatology, Moscow, Russia*
[4] *Royal National Hospital for Rheumatic Diseases, Bath, UK*
[5] *Asturia General Hospital, Oviedo, Spain*
[7] *University Hospital, Leuven, Belgium*
[8] *Aker Hospital, Oslo, Norway*
[9] *Department of Radiology and Nuclear Medicine, Free University, Berlin, Germany*
[10] *Institute of Clinical Medicine, University of Siena, Siena, Italy*
[11] *PKP Medical Centre, Warsaw, Poland*
[15] *The Children Memorial Health Institute, Warsaw, Poland*
[16] *Laboratory for the Research of Musculoskeletal System, University of Athens, Athens, Greece*
[17] *Institute of Rheumatic Diseases, Piestany, Slovakia*
[19] *National Institute of Rheumatology and Physiotherapy, Budapest, Hungary*
[20] *Department of Medicine and Therapeutics, University of Aberdeen, Aberdeen, UK*
[22] *Department of Internal Medicine, Charles University, Prague, Czech Republic*
[23] *School of Nursing, Midwifery and Health Visiting, University of Manchester, Manchester, UK*
[24] *Department of Medicine, University Hospital, Graz, Austria*
[25] *Department of Rheumatology, Royal Cornwall Hospital, Truro, UK*
[**] *Project co-ordinators*

Corresponding Author

Stephen Kaptoge
Strangeways Research Laboratory
Wort's Causeway
CAMBRIDGE CB1 8RN
UK
Tel. +44 1223 741619
Fax. +44 1223 741618
E-mail. stephen@srl.cam.ac.uk

Abstract

We have previously shown that centre and sex specific fall rates explained one third of between centre variation in upper limb fractures across Europe. In this current analysis our aim was to determine how much of the between centre variation in fractures could be attributed to repeated falling, BMD, and other risk factors in individuals, and to compare the relative contributions of centre-specific BMD vs. centre-specific fall rates. A clinical history of fracture was assessed prospectively in 2,451 men and 2,919 women aged 50-80 from 20 centres participating in the European Prospective Osteoporosis Study (EPOS) using standardised questionnaires (mean follow up = 3 years). Bone mineral density (BMD, femoral neck & trochanter and/or spine) was measured in 2,103 men and 2,565 women at these centres. Cox-regression was used to model the risk of incident fracture as a function of the person-specific covariates: age, BMD, personal fracture history (PFH), family hip fracture history (FAMHIP), time spent walking/cycling, number of 'all falls' and falls not causing fracture ('fracture-free') during follow-up, alcohol consumption and body mass index. Centre effects were modelled by inclusion of multiplicative gamma distributed random effects, termed centre shared frailty (CSF), with mean 1 and finite variance theta (θ) acting on the hazard rate. The relative contribution of centre-specific fall risk and centre-specific BMD on the incidence of limb fractures were evaluated as components of CSF.

In women the risk of any incident non-spine fracture (n=190) increased with age, PFH, FAMHIP, >=1hr/day walking/cycling and number of 'all falls' during follow-up (all $P<0.074$). 'Fracture-free' falls ($P=0.726$) and femoral neck BMD did not have a significant effect at the individual level but there was a significant centre shared frailty effect ($\theta = 0.271$, $P=0.001$) that was reduced by 4% after adjusting for mean centre BMD and reduced by 19% when adjusted for mean centre fall rate. Femoral trochanter BMD was a significant determinant of lower limb fractures (n=53, $P=0.014$) and the centre shared frailty effect was significant for upper limb fractures ($\theta = 0.271$, $P=0.011$).

This upper limb fracture centre effect was unchanged after adjusting for mean centre BMD but was reduced by 36% after adjusting for centre mean fall rates.

In men, risk of any non-spine fracture (n=75) increased with PFH, fall during follow-up (P<0.026) and with a decrease in trochanteric BMD [RR 1.38 (1.08, 1.79) per 1SD decrease]. There was no centre effect evident ($\theta = 0.081$, P=0.096).

We conclude that BMD alone cannot be validly used to discriminate between the risk of upper limb fractures across populations without taking account of population-specific variations in fall risk and other factors. These variations might reflect shared environmental or possibly genetic factors that contribute quite substantially to the risk of upper limb fractures in women.

Keywords: Falls, Prospective study, Epidemiology, Osteoporosis, Incident limb fractures, Bone Mineral Density.

Introduction

Aside from major trauma, the occurrence of many limb fractures in those over age 50 is explained by a fall. Those with low bone mineral density (BMD) are at increased risk of fracture as a result of a fall. As argued frequently elsewhere, anticipated risk factors for limb fractures would thus include those associated with both falling and low bone density, including some such as frailty, that might be common to both.

In some prospective studies a decreased bone density has been shown to be an important predictor of future limb fractures. In the Study of Osteoporotic Fractures (SOF), women in the lowest quintile of distal radius BMD had 4 times the risk of distal forearm fracture and 7.5 times the risk of proximal humerus fracture when compared to those in the highest quintile [1]. In the Dubbo study there was a 50% increased risk of forearm and wrist fracture per standard deviation reduction in femoral neck BMD, which was observed in both genders [2]. Some retrospective data suggest that low BMD may be of less importance in predicting susceptibility in those aged over 65 [3] while other data support its utility [4]. The data are not entirely consistent with regard to lifestyle risk factors [2, 5-7], with roles of varying importance for physical inactivity, smoking, body mass and co-morbidity. Some studies have demonstrated a decreased risk of lower limb fracture among the physically active [8, 9] while other studies have shown that the most active persons are at greater risk of an upper limb fracture [1, 10]. Although there is evidence that BMD is important in determining limb fractures, little is known about its relative importance if adjusted for fall risk and other risk factors, especially with data from diverse populations where large variations in BMD and fall risk are to be expected.

We have recently completed a multi-centre multinational prospective study of fractures and falls, the European Prospective Osteoporosis Study, in which non-spine fractures were identified prospectively over a mean of 3 years and spine fractures over a mean of 3.8 years. In recent papers we have presented the descriptive epidemiology of the non-spine fractures [11], an analysis of the

contribution of centre-specific fall rates to the risk of limb fractures [12] and an evaluation of the contribution of lifestyle, gynaecological and fracture history to the risk of distal forearm fracture [13]. In the present paper we have taken advantage of the fact that 20 of the 31 participating centres in the EPOS limb fracture study obtained measurements of hip and/or spine BMD. We have analysed the independent contributions of bone density, falls, and other risk factors for limb fractures with a view to defining their importance for predicting upper and lower limb fractures in European women and men in the 6^{th} to 8^{th} decades of age. We also aimed to describe the relative contributions of centre-specific BMD vs. centre-specific fall rates in explaining variation in fracture rates between centres after adjusting for the risk factors measured at the individual level.

Subjects and methods

Subjects

The subjects included in the analysis were participants in the European Prospective Osteoporosis Study (EPOS), which was a follow-up study on subjects initially recruited to the European Vertebral Osteoporosis Study (EVOS). Detailed methods of the two studies have been reported elsewhere [11, 14, 15]. In brief, stratified sampling was used to recruit men and women aged 50 years and over from population registers in 36 European centres. The aim was to recruit equal numbers of men and women in each of six 5-year age-bands: 50-54, 55-59, 60-64, 65-69, 70-74 and 75+ years. Those who took part had an interviewer administered questionnaire and lateral spine radiographs performed at baseline (the EVOS study).

Subjects from 31 centres were followed prospectively (the EPOS study) by annual postal questionnaire, and were asked to record the occurrence of any incident fractures and the occurrence and number of falls since the baseline survey or the previous postal contact. Self-reported fractures were confirmed where possible, by review of the radiographs, medical record or subject interview. The validity of this approach to fracture definition has been reported elsewhere [16]. Subjects from

20 of these centres also undertook bone mineral density (BMD) measurements on from 10-100% of their available subjects.

Bone mineral density measurements

The densitometers in each centre were, with one exception (a Sopha fan-beam machine), pencil beam dual-energy X-ray absorptiometry (DXA) machines made by Lunar, Hologic or Norland. They were cross-calibrated using the European Spine Phantom [17]. The ESP is a semi-anthropomorphic phantom with three "vertebrae" of known densities 0.5, 1.0 and 1.5g/cm^2 [17]. At least 5 measurements of the phantom were made on each machine and a two-parameter empirically fitted linear or exponential calibration curve used to convert measured density values into standardised values, as described by Pearson [18]. Detailed descriptions of the densitometry procedures as they applied to the subjects are presented elsewhere [19, 20].

Incidence of falls and classification of fractures

Centre-specific incidence of falls was determined by dividing the total number of falls reported by subjects in an individual centre by the person years at risk as reported previously [12]. Because there may be recall bias for falls related to fracture incidence, fall incidence was also estimated using 'fracture-free' falls, which were defined as reported falls that occurred without causing a fracture. The centre 'fracture-free' fall rate was calculated by subtracting the number of fractures from the number of falls reported, then summing over all individuals in the centre and dividing by the person years at risk. The incidences of falls, ('all' and 'fracture free' falls) were calculated by centre, age group and sex. Age-standardised incidence of falls in each centre was calculated using a standard European population [21]. Fractures were classified using the 9th edition of the

International Classification of Diseases (ICD) [22] and analyses were undertaken using any non-spine, upper limb and lower limb fracture categories as response variables.

Statistical analysis

Cox proportional hazard modelling of the risk of fracture was undertaken at the level of the individual subject using Stata version 8 statistical software [23, 24]. Subjects contributed follow-up time (years) from the date of the baseline survey until the first occurrence of the individual limb fracture type (any non-spine, upper limb, or lower limb), death, or the censor date (date of the last questionnaire). Men and women were analysed separately.

Determinants of incident fracture were first assessed using questionnaire variables since this allowed us to use data from a larger number of subjects, i.e. including those who may not have had BMD measurements (these are presented in the results as model 1 and model 2). Later, BMD (from one of the three regions measured) was included as a co-variable in a model that was adjusted for variables that were significant using the larger data set. The variables assessed were: age, family (mother or father) history of hip fracture, personal history of any low or moderate trauma fracture after age 20years (yes vs. no), hours per day spent walking/cycling (>=1hr vs. <1hr), current alcohol consumption as days/week on which alcohol was consumed, body mass index (kg/m^2), and falls reported during follow up (0, 1, 2 or 3+). These were sequentially entered into the model if the likelihood ratio test indicated an effect that was significantly different from zero at the 5% significance level.

To allow for the possibility that time to failure (fracture) for subjects within the same centre may be correlated, a shared centre frailty (or random effect) term that acts multiplicatively on the hazard rate for all individuals within a centre was included in the Cox-regression model (see appendix). The relative importance of BMD vs. falls in explaining incidence of limb fractures was evaluated by comparing estimates of the frailty variance in a series of models (models 3 to 6) as well as fixed

effects estimates. First a reference model (model 3) that included all significant predictors measured at the individual level plus BMD was fitted. Next, the mean centre level BMD was added to the reference model and an estimate of the frailty variance was obtained (model 4). In a third model, centre and sex-specific fall rates were substituted in place of centre level BMD and the frailty variance was similarly obtained (model 5). Finally both centre level BMD and centre and sex-specific fall rates were included in the same model (model 6). For ease of interpretation, the change in the frailty variance was expressed as a percentage of the frailty variance in the reference model (model 3). The model that had a greater reduction in the centre shared frailty variance compared to the reference model was regarded as the more parsimonious one. First all non-spine fractures were modelled, followed by upper limb fractures and finally lower limb fractures.

Results

Subjects characteristics

In the 20 centres which contributed data to this analysis, 2,451 men, mean age 63.7 (SD=8.0) years and 2,919 women, mean age 62.8 (SD=7.7) years were followed for a median of 3.0 years (range = 0.5 to 5.4 years), for a total of 16,654 person years (pyrs) of follow up. Owing to resource constraints, not all centres recruited their target numbers of subjects. Table 1 shows summary statistics for other subject characteristics studied. Bone mineral density was measured at the hip in 2,565 (88%) women and 2,101 (86%) men from 18 centres and was measured at the spine in 2,071 (71%) women and 1,927 (77%) men from 14 centres. The age-standardised incidence of falls by centre in men and women was reported in our previous analyses [12].

Incidence of fractures

For the subjects from the 20 centres participating in the present analysis, the number of incident limb fractures by gender is shown in Table 2. The number of upper limb and lower limb fractures in men were too small to enable precise estimation of risk separately and so the influence of the risk factors considered was determined by modelling only the risk of any non-spine fracture in men. Depending on the occurrence of missing values in the covariates included in the Cox-regression models, the actual number of fracture cases used in the models were slightly lower than shown in Table 2.

Determinants of incident limb fracture in women – models without BMD

Table 3 shows the determinants of incident limb fracture in women from using questionnaire data in the larger dataset without BMD. Variables measured at the individual level were first examined and thereafter centre fall rates were adjusted for as a centre characteristic. Fall history was modelled both as 'all falls' reported during follow-up (Model 1) and also as 'fracture-free' falls (Model 2). The risk of any non-spine fracture significantly increased with age, personal history of any fracture, family history of hip fracture and walking/cycling for >=1hr/day. The significance of the latter two variables was borderline, but were retained in the model since they were independently predictive of upper and lower limb fractures. The risk of any non-spine fracture also differed significantly according to the average number of 'all falls' reported during the 3-year follow up. Compared to subjects who reported falling once, those who did not report a fall had lower risk of fracture as expected, but surprisingly those who reported multiple falls also had lower risk of any non-spine fracture compared to the single fallers. There was a significant centre effect (shared frailty variance = 0.251, $P<0.0001$) and adjustment of centre fall rates, either as 'all falls' or 'fracture-free' fall rates, did not seem to change significance of this centre frailty effect (usually interpreted as being an effect due to some omitted covariate(s) in the Cox-model).

Determinants of upper limb fracture were similar to those of any non-spine fracture, with the exception of personal history of any fracture that failed to be significantly predictive when entered into the model [RR 1.27 (0.81, 2.02) P=0.287]. The nature of the association with number of 'all falls' reported was also similar to that seen for any non-spine fracture, i.e. significantly lower risk in those with none and multiple falls compared to single fallers. There was a significant centre effect (shared frailty variance = 0.244, P=0.004) that did not change after adjustment for the centre fall rates. In contrast to the upper limb, for lower limb fracture, only personal history of any fracture and number of 'all falls' reported during follow up were significant determinants. There was no evidence of a significant centre effect for lower limb fractures.

Because there may be recall bias for falls related to fracture incidence, we repeated the modelling substituting 'fracture free' falls in place of 'all falls' (Model 2). There was no significant association found at the individual level between number of 'fracture-free' falls and incidence of any non- spine, upper limb or lower limb fractures (P>0.595). There was a significant centre effect for any non-spine fracture (shared frailty variance = 0.236, P=0.001) that was reduced to 0.163 (a 31% reduction), after adjusting for centre 'fracture-free' fall rates – this smaller estimate was however still significantly different from zero (P=0.026). In contrast, for upper limb fractures, the centre frailty effect was reduced from an initially significant 0.222 (P=0.015) value to a non-significant 0.146 (P=0.070) value, a 34% reduction, after adjusting for centre 'fracture-free' fall rates. There was no significant centre effect on incidence of lower limb fracture.

Determinants of incident limb fracture in women – models with BMD

Table 4 shows the results from a series of models fitted using data from the smaller sample of subjects who had both questionnaire and BMD data. The objective was to evaluate the relative importance of BMD vs. falls adjusted for other questionnaire variables in explaining incidence of limb fractures. Model 3 was the reference model that included effect of femoral neck BMD

adjusted for other questionnaire variables measured at the individual level that were significantly predictive of limb fracture risk in the larger sample (Table 3). In models 4, 5 and 6, measured centre characteristics were further adjusted for i.e. centre mean femoral neck BMD (in model 4); centre mean fall rate (in model 5) and both centre mean BMD and fall rate (in model 6, footnote). In all models, other unmeasured centre effects were controlled for by inclusion of the centre shared frailty effect.

A decrease in femoral neck BMD was not significantly associated with increased risk of any non-spine fracture [RR 1.13, 95% CI (0.94, 1.35) per 1SD decrease] after adjusting for age, personal fracture history, family hip fracture history, walking /cycling and 'fracture-free fall' during follow-up. There was evidence of a significant centre effect in this model (shared frailty variance = 0.271, P=0.001 model 3). Adjustment of centre mean femoral neck BMD as a centre characteristic was not very efficacious in reducing this unexplained centre effect (shared frailty variance = 0.259, P=0.002 model 4), a reduction of 4% compared to model 3. Inclusion of centre mean 'fracture-free fall' rate as a centre characteristic produced a comparatively larger reduction in the centre shared frailty variance [from 0.271 to 0.220 (19% reduction)], but this smaller estimate was still significantly different from zero (P=0.008 model 5). Adjustment for both centre mean BMD and centre mean fall rate did not result in a substantially greater reduction of the centre shared frailty variance (estimated to be 0.219 (SE 0.156), P=0.008 model 6).

There was no evidence of a significant effect of femoral neck BMD on the risk of upper limb fracture [RR 1.16, 95% CI (0.90,1.51) per 1SD decrease] after adjusting for positive effects of age, family hip fracture history, walking /cycling and 'fracture-free fall' during follow-up. There was however evidence of a significant centre effect (shared frailty variance = 0.271, P=0.011 model 3), which still remained the same when centre mean femoral neck BMD was adjusted for as a centre characteristic (model 4). In contrast, adjustment for centre mean fracture-free fall rate (in model 5) produced a much larger reduction in the centre shared frailty variance [from 0.271 to 0.173 (36% reduction)], which wasn't significantly different from zero (P=0.061). Adjustment of both centre

fall rate and centre mean femoral neck BMD gave a slightly smaller estimate of frailty variance (0.157 (SE 0.166), P=0.080 model 6).

There was no evident association between femoral neck BMD and risk of incident lower limb fracture [RR 1.24 95% CI (0.92, 1.67) per 1SD decrease P=0.154] adjusted for previous fracture history and 'fracture-free fall' during follow-up. Also in contrast to the models for any non-spine and upper limb fracture, there was no evidence of a significant centre effect for lower limb fracture (P=0.065).

When the modelling was repeated with trochanter BMD substituted in place of femoral neck BMD, the results for any non-spine fracture and upper limb fracture did not change. For lower limb fracture, trochanter BMD appeared to have a stronger association than that found earlier with femoral neck BMD. The risk of lower limb fracture increased by 1.45 95% CI (1.08, 1.96) per 1SD decrease in trochanter BMD adjusted for previous fracture history and 'fracture-free fall' during follow-up. As before, there was no centre effect found for lower limb fractures. The risk of any non-spine, upper limb or lower limb fracture was not significantly associated with spine BMD.

Fig. 1 shows the estimated centre shared frailty coefficients for any non-spine fracture and upper limb fracture in models 3, 4, 5 and 6. These are the coefficients used to multiply the hazard rate for all individuals within the same centre such that coefficients < 1 indicate centres with lower frailty and those >1 indicate centres with higher frailty. The figure visually shows the effect of adjusting for centre mean BMD (model 4), centre fall rate (model 5) or both (model 6) in comparison to the reference model with individual level covariates only (model 3). The centres have been ranked according to the estimated frailty in the reference model 3. In most centres, the frailty coefficient remained the same as in the reference model after adjusting for centre femoral neck BMD. In contrast there was a greater tendency for the centre frailty coefficients to increase/reduce towards 1 when centre mean fall rate was adjusted for (model 5), and this was more evident in the case of

upper limb fracture. This further confirms the inferences made from the estimated shared frailty variances in Table 4.

Determinants of incident limb fracture in men

In modelling with questionnaire variables, the risk of any non-spine fracture in men (n=2232, 75 fracture cases) was associated with personal fracture history [RR 1.94 95% CI (1.08, 3.46)] and number of 'all falls' during follow up [RR 0 vs. 1 fall 0.06 (0.03, 0.10); 2 vs. 1 fall 0.40 (0.20, 0.81); and 3+ vs. 1 fall 0.24 (0.11, 0.53)]. The 'fracture-free' falls did not have a significant effect on fracture incidence in men. There was no evidence of a centre effect [shared frailty variance = 0.081 (SE 0.086) P=0.096]. When BMD was added, trochanter BMD had an effect that was independent of personal fracture history and 'fracture free falls' during follow up [RR 1.38 (1.08, 1.79) P=0.012, per 1SD decrease], but was borderline significant in a model with 'all falls' [RR 1.29 (0.99, 1.68) P=0.063, per 1SD decrease]. There were 1888 subjects of whom 63 were fracture cases in the models with trochanter BMD. There was no significant association found with femoral neck and spine BMD (P>0.090).

Finally, since some studies have suggested possible interaction between fall history and BMD in determining fracture incidence [25, 26], we felt the need to assess what evidence our data provided on this hypothesis by testing for interactions. Any such interactions would have suggested different risk gradients per 1SD decrease in BMD in the 0, 1, 2 or 3+ fall frequency categories. For the respective fracture types modelled in each gender (male: any non-spine; female: any non-spine, upper limb, lower limb), we did not find any significant interactions between BMD at any of the three measured sites (femoral neck, trochanter or spine) with number of 'all falls' or 'fracture-free falls' during follow-up (P>0.05 all interactions).

Discussion

Bone mineral density has been shown to be a predictor of fracture in a number of single centre studies. The paper presents data from a multi-centre multinational prospective study. In this paper we present the results of modelling limb fracture risk as a function of BMD after adjusting for the other significant risk factors for fracture described by Silman [13] or Roy et al [12]. The main result is that bone mineral density appeared to be less important in explaining variations in incidence of upper limb fractures in women across diverse populations in Europe compared to the effect of at least some of these other factors. These included variations in the location-specific risk of falling, personal/family history of fracture or factors that may be associated with the likelihood of falling such as amount of time spent walking/cycling.

There was evidence of a strong centre effect on the risk of non-spine fractures in general and upper limb fractures specifically in women, after adjusting for covariates measured at the individual level (including BMD). We hypothesized that this could partly be attributable to differences in centre-specific fall rates or centre-specific BMD and sought to perform a comparison of the two. The contribution of these population-specific (not person-specific) characteristics in accounting for the unexplained centre effect appeared to be more impressive for centre fall rates than with centre BMD in the models for upper limb and any non-spine fracture. Furthermore, the person-specific risk estimate for upper limb fracture associated with a 1SD decrease in femoral neck BMD was modest (RR=1.2) and not statistically significant when adjusted for other covariates (model 3 - model 6). In contrast our results suggested some intricate association between falls and fracture incidence. When 'all falls' were used in the modelling (Table 3, Model 1), there was a significant association between person-specific reported fall frequency and fractures. The risk profile however did not appear to increase linearly with the number of falls since those with zero and multiple falls were at significantly lower risk than those who reported a single fall. It is possible that multiple fallers may institute personal strategies to prevent further falls that endanger their limbs, hence explaining their lower risk compared to single fallers. The centre and sex-specific fall rates did not

appear to explain much of the centre effect observed in this model adjusted for 'all falls'. In contrast, when the modelling was repeated using only falls that did not cause a fracture i.e. 'fracture-free' falls (Table 3, Model 2), there was no significant effect of the person-specific 'fracture-free' fall frequency on fracture incidence, but the centre and sex-specific 'fracture-free' fall rates appeared to explain much of the centre effect observed in the models. Furthermore, the proportionate reduction in the centre shared frailty variance was greater when centre 'fracture-free' fall rates were adjusted for instead of centre mean BMD (Table 4). There was no significant interaction between reported falls and BMD, which suggested that risk profiles for BMD in fallers vs. non-fallers were not greatly different.

The reasons why people fall more in one location compared to another could not be addressed in this study, which was not designed to measure explanatory variables for falls. Other studies [27-29] have suggested it could be related to environmental factors as well as factors specific to individuals such as presence of co-morbid disease or sensory and neuromuscular impairments. Our study favours the first of these explanations, at least over factors that only affect a small minority of the population such as clinical neuromuscular disease. The degree of between centre variation in the levels of these predisposing factors may serve to explain the between centre differences in incidence of falling and hence fracture incidence. The cut-point we chose to categorise the walking/cycling activity level may be considered relatively high for the oldest individuals we studied, but quite modest for younger individuals in their 50's [30].

Centre-related variations in the interpretation and recall of falls might potentially contribute to variations in reported incidence of falling. Although a standardised questionnaire back translated to the subjects' own language was used to minimise misinterpretation in assessing occurrence of falls, we did not perform any ascertainment on the reported falls and therefore cannot rule out a centre-associated bias of this type. As such we cannot be entirely sure for example that different populations actually define a "fall" in the same way. However, our other study [12] found empirically that there was an important relationship between incidence of fractures and fall rates,

even just considering those falls which the respondents did not consider to have caused a fracture. This means that there was a relationship between fractures and reported falls, which is associated with actual falls. In the present analysis, only if false reporting of falls was correlated with BMD, would our results be confounded. We cannot think of a plausible reason why this should be the case.

In agreement with results from the larger dataset with 30 centres [12], we found that in women, the centre-specific risk of falling was more associated with upper limb fractures (69% of these were distal forearm fractures), and less with lower limb fractures. It is possible that this difference could be explained by the type of fall since for example a sideways fall onto the hip is more likely to lead to a hip fracture while a fall onto the hand, particularly when the subject is moving at full walking speed or faster [31], is more likely to lead to distal forearm fracture. If there was a greater between-centre variability in falls overloading the upper limb than the lower limb, then this may explain why fall rates were more associated with upper limb fractures. We could not however test this since no information was collected about the type of fall. Because of incomplete data from the centres concerning level of trauma during fracture, we were unable to determine whether distinguishing between high or low trauma fractures could have altered the association between fracture and bone mass. However, there is also evidence that low bone mass also contributes to high trauma fracture in those over 50 years [32].

Interestingly, for any non-spine fracture, there was still a residual centre effect that was not accounted for by adjustment of person-specific covariates, centre level BMD and centre fall rates. In addition to variation in fall incidence, geographic differences in genetic profiles that contribute to fractures could potentially explain the geographical or centre-related differences in limb fracture incidence. There is for example evidence that the collagen I-alpha 1 (COLIA1) Sp1 gene polymorphism influences risk of prevalent fractures [33], though the evidence seems to be stronger for vertebral fractures. Weichetova et al [34] demonstrated that COLIA1 Sp1 polymorphism was associated with an increased risk of wrist fracture in postmenopausal women independent of BMD.

Women with *Ss* heterozygous genotype had 2 times the risk of women with *SS* homozygous genotype and women with *ss* homozygous genotype had 2.8 times the risk of women with *SS* homozygous genotype. The overall gene-dose effect was an odds ratio of 2.1 per copy of the "*s*" allele. These results suggest that known geographical differences in the prevalence of the "*s*" allele could contribute to differences in fracture incidence.

This study has implications for developing prevention strategies. Previous data has linked falls to both hip fracture and upper limb fracture. Whereas the direction of falling is more likely to be sideways for a hip fracture, an upper limb fracture is usually caused by a forward fall. While it is by no means clear that risk factors for these different types of fall are similar, the present study and its predecessor [12] suggest that more information is needed on the causes of the geographic variability of fall rates if generally effective prevention strategies are to be developed.

In conclusion, our results have demonstrated important limitations in the role of BMD in predicting the risk of non-spine fractures across populations. In particular for upper limb fractures there was a much more significant effect of the risk of falling on fracture risk than of BMD. This suggests that models for fracture risk based on BMD and other data obtained in comparatively homogeneous populations should be treated with caution if it is desired to extrapolate to different populations. Therefore in many communities around the world there may well remain a continuing need for developing risk models based on locally valid data of the type we have obtained in this study, in support of improved prevention and management strategies for fractures. In clinical practice, these findings emphasise the increasingly recognised need for developing risk models that include non-BMD related risk indicators alongside BMD. These now include for upper limb fractures in women population-specific risks of falling. There is also encouragement to study further the contribution of environmental hazards leading to limb fracture in women over 50 years.

Word Count: Text = 4,804

Acknowledgements

The study was financially supported by a European Union Concerted Action Grant under Biomed-1 (BMH1CT920182), and also EU grants C1PDCT925102, ERBC1PDCT 930105 & 940229. The central coordination was also supported by the UK Arthritis Research Campaign, the Medical Research Council (G9321536), and the European Foundation for Osteoporosis and Bone Disease. The EU's PECO program linked to BIOMED 1 funded in part the participation of the Budapest, Warsaw, Prague, Piestany, Szczecin and Moscow centres. The remaining funding was provided by or through the following centers: *Co-ordination and Data Evaluation Centers*: University of Cambridge, Institute of Public Health, Cambridge, U.K (SK, JR, CJT, ML) and ARC Epidemiology Unit, University of Manchester, U.K (AJS, TWO'N, ML, AAI, JDF)*; Participating Investigative Centers:* Institute of Rheumatology, Moscow, Russia (LIB); Royal National Hospital for Rheumatic Diseases, Bath, U.K (AKB).; Asturias General Hospital, Oviedo, Spain (JBC, MND); University of Southampton, U.K. (CC); University Hospital, Leuven, Belgium (SB); University of Oslo, Aker Hospital (JAF); Department of Radiology and Nuclear Medicine, Free University, Berlin, Germany (DF)*;* Charles University, Prague, Czech Republic (JJS); PKP & Childrens' Hospitals, Warsaw, Poland (KH, RL); Ruhr University, Bochum, Germany (JJ); Medical Academy, Erfurt, Germany (GK); University of Sheffield, U.K.(JAK); University of Athens, Greece (GL); Institute of Rheumatic Diseases, Piestany, Slovakia (PM); Academy of Medicine, Szczecin, Poland (TM); University of Siena, Italy (RN); Erasmus University, Rotterdam, Netherlands (HAPP); National Institute of Rheumatology and Physiotherapy, Budapest, Hungary (GP); University of Aberdeen, U.K.(DMR); University of Heidelberg, Germany (CS-N); University Hospital, Graz, Austria (KW); Royal Cornwall Hospital, Truro, U.K,(ADW).

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Table 1. Subject characteristics

Variable	N	Men Mean (SD) or Proportion	N	Women Mean (SD) or Proportion
Age (yrs)	2451	63.7 (8.0)	2919	62.8 (7.7)
Weight (kg)	2383	79.5 (11.0)	2776	68.6 (11.7)
Height (m)	2383	1.72 (0.07)	2778	1.59 (0.07)
BMI (kg/m^2)	2378	26.9 (3.3)	2774	27.1 (4.5)
Femoral neck BMD (g/cm^2)	2101	0.827 (0.144)	2565	0.728 (0.137)
Trochanter BMD (g/cm^2)	2103	0.768 (0.140)	2565	0.627 (0.124)
Spine BMD (g/cm^2)	1927	1.061 (0.226)	2071	0.923 (0.209)
Personal history of any fracture [a]				
Yes	341	15%	578	21%
No	1907	85%	2141	79%
Total	2248	100%	2719	100%
Family history of hip fracture				
Yes	189	8%	249	9%
No	2055	92%	2465	91%
Total	2244	100%	2714	100%
Time spent walking/cycling				
<1 hr/day	875	39%	1445	53%
>=1hr/day	1386	61%	1280	47%
Total	2261	100%	2725	100%
Average 'all falls' reported during 3-year follow-up				
0 fall	1,852	77%	1,952	68%
1 fall	233	10%	441	15%
2 falls	143	6%	206	7%
3+ falls	192	8%	251	9%
Total	2,420	100%	2,850	100%
Average 'fracture-free falls' during 3-year follow-up				
0 fall	1,895	78%	2,052	72%
1 fall	200	8%	375	13%
2 falls	135	6%	185	6%
3+ falls	190	8%	238	8%
Total	2,420	100%	2,850	100%
Alcohol consumption				
Daily	594	26%	206	7%
5 – 6 days/wk	88	4%	40	1%
3 – 4 days/wk	251	11%	142	5%
1 – 2 days/wk	516	22%	448	16%
< 1 day/wk	569	25%	1014	36%
Never	299	13%	992	35%
Total	2317	100%	2842	100%

[a] Self-reported history of any low or moderate trauma fracture after age 20 years

Table 2. Number and crude incidence of limb fractures by gender

	Men (n = 2,451)			Women (n = 2,919)		
Fracture type	Number of subjects with fractures	Person-years at risk[a]	Crude incidence per 100pyrs (95% CI)	Number of subjects with fractures	Person-years at risk[a]	Crude incidence per 100pyrs (95% CI)
Upper limb	24	7508	0.32 (0.21, 0.48)	102	8959	1.14 (0.94, 1.38)
Lower limb	25	7500	0.33 (0.23, 0.49)	70	8993	0.78 (0.62, 0.98)
Any non-spine[b]	83	7422	1.12 (0.90, 1.37)	221	8768	2.52 (2.21, 2.88)

[a] Total follow up time to first limb fracture of each type, death or end of study

[b] Includes limb fractures unassigned ICD codes and rib fractures

Table 3. Determinants of incident limb fracture in women – models using larger dataset without BMD.

Outcome/Predictors	Model 1 (Modelling with 'all falls') RR (95% CI)	P		Model 2 (Modelling with 'fracture-free' falls) RR (95% CI)	P
Any non-spine fracture (n=2676, 190 fractures)					
Age (per decade)	1.28 (1.06, 1.56)	0.012		1.38 (1.14, 1.67)	0.001
Personal fracture history (yes vs. no)	1.79 (1.31, 2.45)	<0.0001		1.89 (1.39, 2.58)	<0.0001
Family hip fracture history (yes vs. no)	1.49 (0.98, 2.26)	0.060		1.72 (1.14, 2.59)	0.010
Walking/cycling (>=1hr/day vs. <1hr/day)	1.32 (0.97, 1.78)	0.074		1.35 (1.00, 1.83)	0.052
Average falls reported during 3-year follow-up [a]		<0.0001			0.726
0 vs. 1	0.09 (0.06, 0.13)	<0.0001	1 vs. 0	0.80 (0.51, 1.23)	0.308
2 vs. 1	0.81 (0.54, 1.21)	0.308	2 vs. 0	0.82 (0.46, 1.46)	0.504
3+ vs. 1	0.60 (0.40, 0.91)	0.016	3+ vs. 0	0.95 (0.59, 1.55)	0.852
Centre and sex specific fall rates					
'All falls' fall rate (1 fall/person-year)	0.92 (0.19, 4.41)	0.922		3.14 (0.80, 12.28)	0.100
'Fracture-free' fall rate (1 fall/person-year)	0.82 (0.16, 4.28)	0.818		3.05 (0.71, 13.22)	0.135
Estimated centre shared frailty variance (SE) [b, c]					
Adjusted for centre 'all falls' fall rate	0.252 (0.149)	<0.0001		0.152 (0.127)	0.035
Adjusted for centre 'fracture-free' fall rate	0.254 (0.150)	<0.0001		0.163 (0.130)	0.026
Upper limb fracture (n=2686, 94 fractures)					
Age (per decade)	1.48 (1.12, 1.94)	0.006		1.60 (1.22, 2.09)	0.001
Family hip fracture history (yes vs. no)	2.07 (1.20, 3.57)	0.009		2.30 (1.34, 3.95)	0.002
Walking/cycling (>=1hr/day vs. <1hr/day)	1.78 (1.15, 2.77)	0.010		1.90 (1.23, 2.95)	0.004
Average falls reported during 3-year follow-up [a]		<0.0001			0.595
0 vs. 1	0.08 (0.05, 0.15)	<0.0001	1 vs. 0	0.65 (0.34, 1.26)	0.205
2 vs. 1	0.64 (0.35, 1.18)	0.152	2 vs. 0	0.76 (0.33, 1.77)	0.528
3+ vs. 1	0.54 (0.30, 0.97)	0.039	3+ vs. 0	1.00 (0.52, 1.93)	0.996
Centre and sex specific fall rates					
'All falls' fall rate (1 fall/person-year)	1.27 (0.22, 7.41)	0.793		3.73 (0.79, 17.59)	0.096
'Fracture-free' fall rate (1 fall/person-year)	1.17 (0.18, 7.63)	0.869		3.72 (0.71, 19.58)	0.121
Estimated centre shared frailty variance (SE) [b, c]					
Adjusted for centre 'all falls' fall rate	0.240 (0.164)	0.004		0.138 (0.140)	0.079
Adjusted for centre 'fracture-free' fall rate	0.242 (0.165)	0.004		0.146 (0.143)	0.070
Lower limb fracture (n=2695, 63 fractures)					
Personal fracture history (yes vs. no)	2.23 (1.32, 3.75)	0.003		2.39 (1.43, 4.02)	0.001
Average falls reported during 3-year follow-up [a]		<0.0001			0.843
0 vs. 1	0.09 (0.04, 0.18)	<0.0001	1 vs. 0	0.69 (0.30, 1.55)	0.365
2 vs. 1	0.68 (0.33, 1.40)	0.299	2 vs. 0	0.96 (0.38, 2.45)	0.940
3+ vs. 1	0.64 (0.32, 1.31)	0.222	3+ vs. 0	0.94 (0.39, 2.23)	0.883
Centre and sex specific fall rates					
'All falls' fall rate (1 fall/person-year)	0.76 (0.09, 6.24)	0.799		2.72 (0.42, 17.57)	0.293
'Fracture-free' fall rate (1 fall/person-year)	0.66 (0.07, 6.13)	0.713		2.60 (0.35, 19.27)	0.350
Estimated centre shared frailty variance (SE) [b, c]					
Adjusted for centre 'all falls' fall rate	0.247 (0.252)	0.077		0.155 (0.232)	0.198
Adjusted for centre 'fracture-free' fall rate	0.249 (0.253)	0.076		0.166 (0.237)	0.184

[a] The estimates in Model 1 relate to 'all falls' reported, while those in Model 2 relate to 'fracture-free' falls.
[b] The P-value shown is for the test of the null hypothesis that the shared frailty variance is zero, but since variances cannot be negative, estimation of the P-value does not use the standard normal distribution (see appendix for details).
[c] In models not adjusted for centre fall rates the, shared frailty variances (SE) in the modelling with 'all falls' were: any non-spine 0.251 (0.148) P<0.0001; upper limb 0.244 (0.165) P=0.004; lower limb 0.241 (0.247) P=0.079. In the modelling with 'fracture-free falls' the shared frailty variances (SE) were: any non-spine 0.236 (0.144) P=0.001; upper limb 0.222 (0.168) P=0.015; and lower limb 0.243 (0.249) P=0.084.

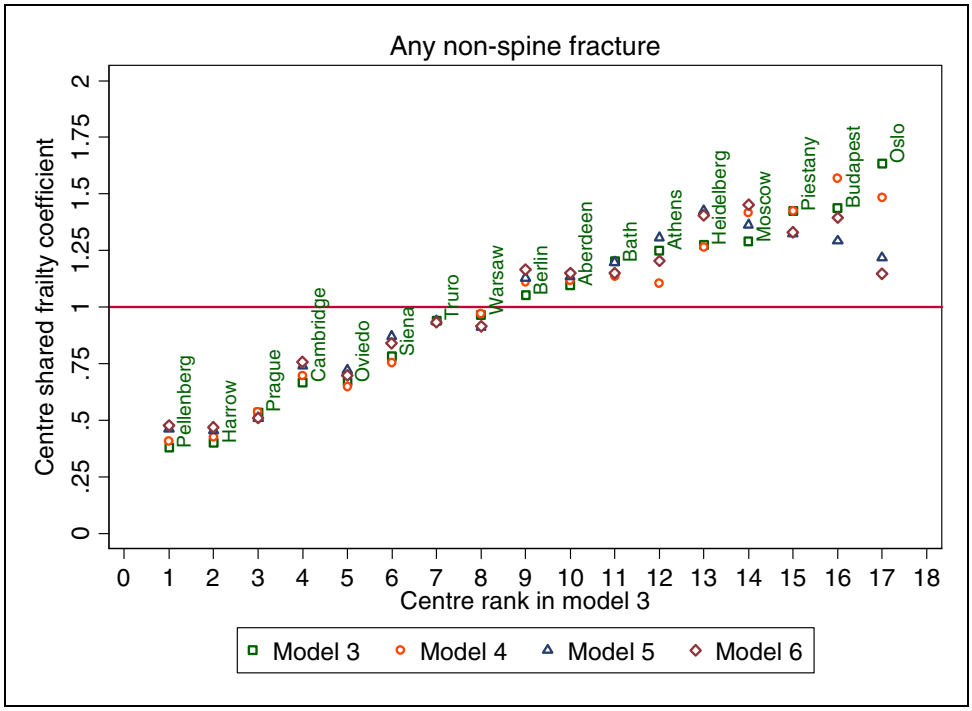
Table 4. Determinants of incident limb fracture in women – models restricted to smaller dataset with BMD measurements.

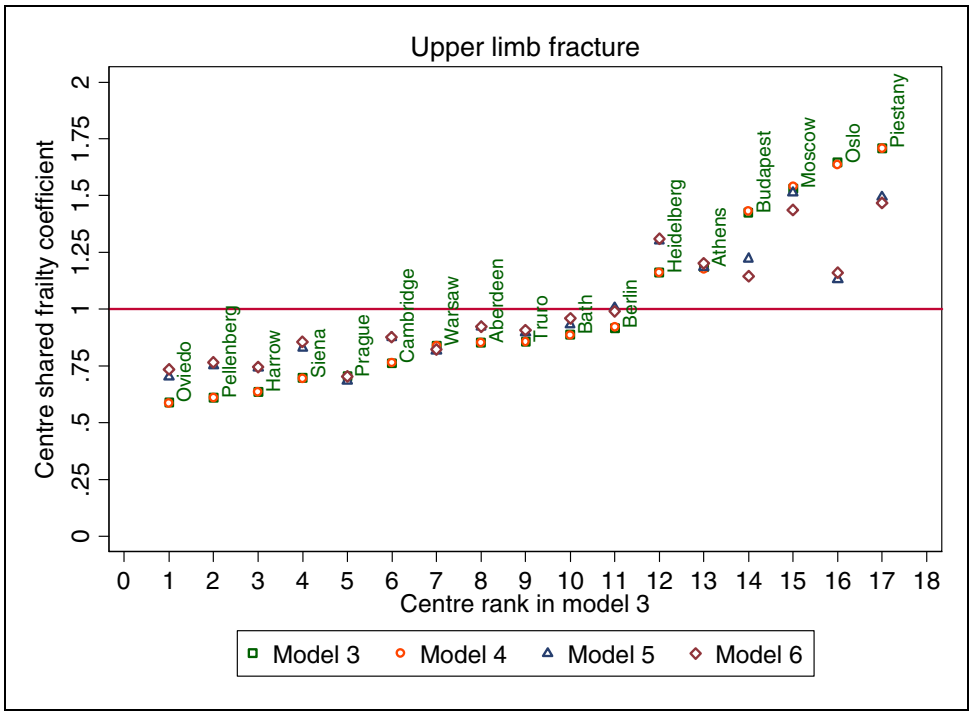
Outcome/Predictors	Model 3 (+ Individual level BMD) RR (95% CI)	P	Model 4 (+ Centre mean BMD) RR (95% CI)	P	Model 5 [a] (+ Centre mean fall rate) RR (95% CI)	P
Any non-spine fracture (n=2328, 155 fractures)						
Age (per decade)	1.29 (1.02, 1.62)	0.031	1.29 (1.02, 1.62)	0.030	1.28 (1.02, 1.62)	0.033
Personal fracture history (yes vs. no)	1.83 (1.30, 2.57)	0.001	1.83 (1.30, 2.58)	0.001	1.82 (1.29, 2.57)	0.001
Family hip fracture history (yes vs. no)	1.72 (1.09, 2.72)	0.020	1.70 (1.07, 2.69)	0.024	1.71 (1.08, 2.70)	0.022
Walking/cycling (>=1hr/day vs. <1hr/day)	1.35 (0.96, 1.89)	0.084	1.37 (0.97, 1.92)	0.074	1.35 (0.96, 1.89)	0.085
Average 'fracture-free falls' in 3-yr follow-up		0.982		0.981		0.978
1 vs. 0	1.05 (0.65, 1.70)	0.833	1.06 (0.65, 1.72)	0.813	1.04 (0.64, 1.69)	0.866
2 vs. 0	0.90 (0.47, 1.74)	0.755	0.90 (0.47, 1.74)	0.763	0.89 (0.46, 1.72)	0.731
3+ vs. 0	0.97 (0.57, 1.67)	0.922	0.97 (0.57, 1.67)	0.918	0.95 (0.55, 1.63)	0.842
Femoral neck BMD (1 SD decrease)	1.13 (0.94, 1.35)	0.200	1.12 (0.93, 1.34)	0.245	1.13 (0.94, 1.35)	0.200
Centre femoral neck BMD (1 SD decrease)	-	-	1.46 (0.49, 4.36)	0.497	-	-
Centre 'fracture-free' fall rate (1 fall/pyr)	-	-	-	-	2.59 (0.48, 14.01)	0.271
Estimated centre shared frailty variance (SE)	0.271 (0.170)	0.001	0.259 (0.165)	0.002	0.220 (0.158)	0.008
% Reduction in shared frailty variance	-		-4%		-19%	
Upper limb fracture (n=2338, 75 fractures)						
Age (per decade)	1.57 (1.13, 2.17)	0.007	1.57 (1.13, 2.17)	0.007	1.57 (1.13, 2.17)	0.007
Family hip fracture (yes vs. no)	2.10 (1.13, 3.89)	0.018	2.10 (1.12, 3.91)	0.020	2.04 (1.10, 3.78)	0.024
Walking/cycling (>=1hr/day vs. <1hr/day)	1.77 (1.08, 2.91)	0.023	1.77 (1.08, 2.91)	0.023	1.76 (1.07, 2.87)	0.025
Average 'fracture-free falls' in 3-yr follow-up		0.907		0.907		0.958
1 vs. 0	1.08 (0.54, 2.15)	0.832	1.08 (0.54, 2.15)	0.830	1.05 (0.53, 2.10)	0.885
2 vs. 0	0.97 (0.39, 2.47)	0.957	0.97 (0.39, 2.47)	0.957	0.95 (0.38, 2.41)	0.920
3+ vs. 0	1.29 (0.64, 2.60)	0.471	1.29 (0.64, 2.60)	0.472	1.21 (0.60, 2.44)	0.601
Femoral neck BMD (1 SD decrease)	1.16 (0.90, 1.51)	0.255	1.16 (0.89, 1.51)	0.267	1.15 (0.89, 1.49)	0.297
Centre femoral neck BMD (1 SD decrease)	-	-	1.04 (0.27, 4.02)	0.960	-	-
Centre 'fracture-free' fall rate (1 fall/pyr)	-	-	-	-	4.45 (0.70, 28.32)	0.114
Estimated centre shared frailty variance (SE)	0.271 (0.203)	0.011	0.271 (0.203)	0.011	0.173 (0.169)	0.061
% Reduction in shared frailty variance	-		0%		-36%	
Lower limb fracture (n=2345, 53 fractures)						
Personal fracture history (yes vs. no)	2.21 (1.25, 3.91)	0.006	2.22 (1.25, 3.92)	0.006	2.21 (1.25, 3.9)	0.007
Average 'fracture-free falls' in 3-yr follow-up		0.444		0.449		0.433
1 vs. 0	0.39 (0.12, 1.27)	0.119	0.39 (0.12, 1.28)	0.122	0.39 (0.12, 1.27)	0.116
2 vs. 0	0.99 (0.35, 2.79)	0.987	0.99 (0.35, 2.80)	0.988	0.98 (0.35, 2.77)	0.971
3+ vs. 0	0.73 (0.26, 2.06)	0.552	0.73 (0.26, 2.06)	0.547	0.71 (0.25, 2.03)	0.525
Femoral neck BMD (1 SD decrease)[b]	1.24 (0.92, 1.67)	0.154	1.22 (0.90, 1.66)	0.190	1.24 (0.92, 1.67)	0.154
Centre femoral neck BMD (1 SD decrease)	-	-	1.41 (0.33, 6.00)	0.644	-	-
Centre 'fracture-free' fall rate (1 fall/pyr)	-	-	-	-	1.60 (0.15, 16.92)	0.694
Estimated centre shared frailty variance (SE)	0.283 (0.279)	0.065	0.290 (0.276)	0.058	0.262 (0.277)	0.085
% Reduction in shared frailty variance	-		2%		-7%	

[a] In a model 6 that was adjusted for both centre mean BMD and centre fall rate, the shared frailty variances (SE) were: any non-spine 0.219 (0.156) P=0.008; upper limb 0.157 (0.166) P=0.080; and lower limb 0.275 (0.275) P=0.075.
[b] Trochanter BMD was a significant predictor of lower limb fracture when substituted in place of femoral neck BMD: RR per 1 SD decrease was 1.45 (1.08, 1.96) P=0.014 in models 3 & 5 and was 1.44 (1.07, 1.94) P=0.017 in model 4 .

Figures

Fig. 1. Estimated centre shared frailty coefficients for any non-spine fracture and upper limb fracture in women.





Key:
Model 3: Adjusted for individual level covariates including individual femoral neck BMD
Model 4: Same as model 3, but further adjusted for mean centre femoral neck BMD
Model 5: Same as model 3, but further adjusted for centre 'fracture-free' fall rates
Model 6: Same as model 3, and adjusted for both centre femoral neck BMD & centre 'fracture-free' fall rates

Appendix

Cox Proportional hazards model with frailties

It is usually assumed in the Cox proportional hazards regression model that survival times for individuals are conditionally independent given the measured covariates adjusted for, in addition to the standard proportional hazards assumption. However in practice it is unlikely that all covariates of interest can be measured, especially in multi-centre studies where factors common to the centre can be difficult to measure, and can therefore cause dependence of for example fracture-free survival times of individuals within a centre. The frailty model is an extension of the traditional Cox regression model that attempts to statistically adjust for this possibility by including an unobservable shared centre frailty (or random effect) term that acts multiplicatively on the hazard rate for all individuals within a centre. Thus for subject j in centre i, with k measured covariates $\mathbf{x}_{ij} = (x_{ij1}, x_{ij2}, \cdots, x_{ijk})'$, the hazard rate at time t is given by:

$$\lambda_{ij}(t \mid \mathbf{x}_{ij}) = \lambda_0(t) u_i \exp(\boldsymbol{\beta}' \mathbf{x}_{ij})$$

Where $\lambda_0(t)$ is the baseline hazard rate at time t and $u_i's$ are the multiplicative centre shared frailty coefficients. Note that the term 'frailty' arises from the early use of this type of models in modelling 'accident proneness' in individuals and has since been regularly used in the statistical literature particularly in relation to chronic disease incidence in families. The frailties are usually constrained to have a gamma distribution with mean 1 and finite variance theta (θ), and thus a test of the null hypothesis of no centre effect is equivalent to testing that the shared frailty variance θ = 0 [35] i.e. all frailties form a mass point at 1. Since θ is a variance, it cannot be negative, and so the null hypothesis H0: θ = 0 is evaluated at the boundary of the parameter space. In such cases the limiting distribution of the maximum likelihood estimate of θ is not asymptotic normal distribution but is rather a normal distribution that is halved or chopped off at zero. As a result the distribution of the likelihood ratio (LR) test statistic is not the usual chi-square with 1 degree of freedom, but is instead a 50:50 mixture of a chi-square with no degrees of freedom (i.e. a point mass at zero) and a

chi-square with 1 degree of freedom. The software takes this into account, and the P-value is set to 1 if it is determined that the variance estimate is close enough to zero to be, in effect, zero for purposes of significance. Otherwise, the p-value displayed is set to one-half of the probability that a chi-square with 1 degree of freedom is greater than the calculated LR test statistic. The frailty approach to testing for centre effects has been shown to maintain nominal levels of significance even when the number of subjects per centre is small in contrast to adjusting for centre as a fixed effect using dummy variables in the Cox-model. The latter approach more often rejects the null hypothesis of no centre effect and requires a large number of subjects per centre to give significance levels close to the nominal value [24]. Furthermore, there should at least be one event occurring in each centre otherwise fixed effects estimates for that centre will not exist.