

Risk Factors for Vertebral and Nonvertebral Fracture Over 10 Years: A Population-Based Study in Women

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ABSTRACT: Risk factors may vary for different types of fracture, in particular for vertebral fractures. We followed 367 women >50 yr of age from a population-based cohort for up to 10 yr. Factors that predicted vertebral rather than nonvertebral fractures related to physical weakness, poor health, and weight loss. Similar factors were also associated with greater bone loss at the hip.

Introduction: Many risk factors predict fractures overall, but it is less clear whether certain factors relate to vertebral fractures in particular. The aim of this study was to compare the risk factors for vertebral and nonvertebral fractures.

Materials and Methods: We carried out a 10-yr prospective population-based study of 375 women who were 50–85 yr of age initially. At baseline, we measured BMD, blood and urine biochemistry, and anthropometric measurements. Medical and lifestyle data were obtained by questionnaire. Incident vertebral fractures were determined for 311 subjects from spinal radiographs at 0, 2, 5, 7, and 10 yr using an algorithm-based qualitative method, and nonvertebral fractures were confirmed radiographically. Relative risks were calculated by Cox regression analysis.

Results: During follow-up, 70 subjects sustained one or more nonvertebral fractures and 29 sustained one or more vertebral fractures. Risk factors that predicted both types of fracture included increasing age, decreasing BMD at all sites, prevalent vertebral fracture, and shorter estrogen exposure. For nonvertebral fractures only, the risk factors included low urinary creatinine and less frequent use of stairs. The factors for vertebral fractures included lighter weight, reduced body fat, heavy smoking, lower serum calcium, albumin, and thyroid T₃, weak grip strength, and poor physical capability. In a multivariate model, weight, fat mass, serum calcium and T₃, prevalent vertebral fracture, and physical capability remained significant. Furthermore, grip strength, serum albumin, weight loss, and physical capability were associated with rate of bone loss at the femoral neck, and a fast rate of bone loss was also associated with vertebral fractures.

Conclusions: We conclude that overall frailty, which may consist of general poor health, small or thin body size, and lack of strength and physical capability, predicts vertebral fractures but is not a significant predictor of nonvertebral fractures. Bone loss rates are associated with similar risk factors and also with the incidence of vertebral fractures.

J Bone Miner Res 2008;23:75–85. Published online on September 3, 2007; doi: 10.1359/JBMR.070814

Key words: vertebral fracture, nonvertebral fracture, risk factors, osteoporosis, frailty

INTRODUCTION

IT IS IMPORTANT to be able to identify those at highest risk of future fracture to best target preventative measures. Some risk factors such as BMD, if available, and age are strongly predictive of all types of fracture, as established by many studies.^(1–5)

Other risk factors may vary according to fracture site,^(6–8) as may the precipitating event. At least 90% of hip fractures result from a fall, whereas falls precede only ~25% of vertebral fractures, with many resulting from apparently insignificant everyday activities.^(9,10) A number of studies of

fracture prediction have investigated the particular risk factors for hip fracture,^(11–13) because these are generally considered to have the most serious impact. However, many investigations have considered all types of “osteoporotic” fracture together or have not included vertebral fractures unless symptomatic and clinically diagnosed.^(2,14) These approaches can obscure or weaken the predictive value of a risk factor for a particular type of fracture, such as vertebral fracture. There is evidence that vertebral fractures are associated with increased morbidity and loss of function and mortality, to an extent that may be comparable in the long-term with the outcomes of hip fractures.^(15–19)

We have carried out a 10-yr longitudinal population-based study of 375 women, 50–85 yr of age, with spine

The authors state that they have no conflicts of interest.

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radiographs at five time-points. Comprehensive data collection included BMD, biochemistry, reproductive and medical history, personal and family fracture history, lifestyle, anthropometric measurements, and incident vertebral and nonvertebral fractures.

The objective of this analysis is to study whether there is a group of risk factors that predict vertebral fractures in particular and to examine rates of bone loss and their relationship, if any, to vertebral fracture.

MATERIALS AND METHODS

Subjects

We recruited 375 women, 50–85 yr of age, randomly from three general practitioner (GP) lists in Sheffield, UK, between July 1990 and October 1991, as previously described.⁽²⁰⁾ The socioeconomic distribution of the participants was representative of Sheffield as a whole. The uptake rate was 55% of those invited to participate. The only reasons for exclusion were that a subject was too ill to take part or was unwilling or unable to consent.

The distribution of subjects' ages by decade was as follows: 137, 134, 76, and 28 subjects were recruited in the age bands 50–59, 60–69, 70–79 and 80–85 yr. Study visits were at 0, 2, 5, 7, and 10 yr, and the numbers attending these visits were 375, 310, 242, 196, and 182, respectively. There were 66 subjects who died during the study.

Incident fractures

Information about nonvertebral fractures was obtained in a number of ways: GP medical notes for all subjects were examined at 5 yr; medical notes for 61 subjects who had died were available for examination at 10 yr; data were acquired from questionnaires at the final 10-yr visit; and request forms were sent out to 106 subjects who did not attend at 10 yr, of which 86 were returned.

Nonvertebral fractures were included only if confirmed by radiologist's report or orthopedic notes. Fractures at all sites were included, whether or not caused by "low trauma." Eight subjects were lost to follow-up and had no further fracture data available after the baseline visit, leaving a maximum 367 subjects for incident fracture analysis. The median time of follow-up (or to first fracture) was 10.0 yr, with a range of 0.1–11.3 yr. Vertebral fractures were included only if confirmed by lateral spine radiograph, as part of a study visit, and the visit date on which the fracture was first seen was taken as the "date of fracture." Vertebrae T₄ to L₅ were included in the analysis. Radiographs of all prevalent and incident fractures were read and evaluated by a single radiologist, using an algorithm-based qualitative method (ABQ): a systematic approach to the identification of fractures based primarily on changes in the vertebral endplate, not simply a reduction in vertebral height.⁽²¹⁾ The median time of follow-up was 10.0 yr, with a range of 1.9–11.3 yr. There were 61 subjects who had no further radiographs after the baseline visit.

BMD measurements

These were performed using DXA by Lunar DPX densitometer (Lunar, Madison, WI, USA). At baseline, BMD

was measured at the lumbar spine (LS), femoral neck (FN), and total body (TB). The short-term in vivo CVs in 20 women were 1%, 3%, and 1%, respectively. Quality assurance was carried out by means of daily measurements of an aluminium spine phantom. There was some evidence of variability and shifts, particularly after two detector changes, but over the whole study period, 95% of these measurements were within the mean \pm 1.6%. No correction factors were applied. Body composition (fat and lean mass) was also measured by DXA. The scans were analyzed using Lunar software version 3.6.

Change in BMD

The annual rate of change in BMD at the FN was calculated for those subjects that attended for BMD measurements for at least 5 yr from baseline ($n = 254$). It was based on the gradient of the regression line for each subject's FN BMD at every visit made and calculated as a percentage of the baseline BMD value. The rate of LS BMD change was similarly calculated.

Biochemical measurements

At baseline, blood samples were taken in the fasting state between 9:00 a.m. and 9:45 a.m., and a 24-h urine collection was completed. Serum measurements included calcium, creatinine, phosphate, alkaline phosphatase, intact PTH, albumin, and thyroid hormones total and free T₄, total T₃, and thyroid-stimulating hormone (TSH). Urine was analyzed for calcium and creatinine, and 24-h volume was measured. All analyses were carried out by the Clinical Chemistry Laboratory at the Northern General Hospital, Sheffield, UK, using standard methods.

Anthropometric measurements

Height and body weight were measured in light clothing, without shoes. Height was measured to the nearest centimeter using a wall-mounted stadiometer, and weight was measured to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight (kg)/height (m)². Grip strength was also measured in triplicate for each hand, taking the best result, using a grip dynamometer (Accoson, London, UK).

Changes in weight and body composition

Weight, fat mass, and lean mass changes during the study were calculated from the difference between baseline and last measurements, as a percentage of baseline. These were converted to an annual rate to take account of duration of participation. Rates of change were available for the 314 subjects with a follow-up visit.

Medical and lifestyle history

A standardized medical and lifestyle questionnaire was administered by interview at baseline.⁽²²⁾ Further in-house questionnaires were completed at subsequent visits. Data collected included reproductive, medical, fracture, and medication history, and lifestyle details including diet, smoking, alcohol, and exercise habits and history. Subjects were asked to self-rate their own health and to assess the degree of difficulty on a scale of 1–3 they would experience in carrying out a range of activities. Dietary calcium intake

was estimated by a food frequency questionnaire in those who returned at 2 yr ($n = 310$). This was previously validated against a 4-day weighed intake in 30 postmenopausal women ($r = 0.68$).⁽²³⁾

At the first follow-up visit at 2 yr, we asked questions on current medications and recent surgery. We made an estimate of comorbidities by counting prescription medications and combining with a point score (0–3) from minor or significant surgical operations.

Data analysis

Comparisons of baseline characteristics between groups of subjects were made by *t*-tests, Mann-Whitney tests, or χ^2 tests. Correlations between variables were assessed by Pearson's or Spearman's methods. Relationships between possible predictor variables and incident vertebral or nonvertebral fractures were analyzed by Cox proportional hazards regression. Predictors for vertebral fractures and for nonvertebral fractures were analyzed separately, because of the differing methods of determining time of fracture. Survival time was taken to first fracture for each subject and nonfracture cases were censored at the date that the latest information was available or date of death. Variables found to be significant in a univariate model were entered into multivariate models with age and/or BMD using forward stepwise Wald analysis to assess their independence, with $p < 0.05$ as the criterion for inclusion. Finally, all individually significant predictors were entered into a multivariate model for each fracture type, without stepwise exclusion. Binary logistic regression, with forward stepwise analysis for multiple factors, was used to assess relationships between rates of change and incident fracture. A weighted risk score was calculated as follows, by a method similar to that of Black et al.⁽³⁾ Age-independent risk factors were entered into a multiple logistic regression model, with continuous variables dichotomized by highest risk quartile. The resulting regression coefficients were used to weight these binary risk factors, and an additive risk score was generated by doubling the sum, adding 1, and rounding to an integer value. Statistical analysis was performed by SPSS (Chicago, IL, USA).

RESULTS

Baseline characteristics of the 367 subjects that had follow-up fracture data and formed the cohort for the fracture analyses are shown in Table 1. The characteristics of the subjects who returned for at least one further visit after the start of the study ($n = 314$) were compared with those who did not ($n = 61$). The significant differences between the two groups were in age, current smoking status, and corticosteroid use. Those who did not make a return visit were older (67.8 versus 63.9 yr, $p < 0.01$), more likely to be smokers (34% versus 18%; $p < 0.01$), and more likely to have ever taken oral steroids (10% versus 4%; $p = 0.035$).

At baseline, 13 (4%) of the 367 women were still premenopausal. At 2 yr, only 3 had not yet gone through the menopause, and by 5 yr, there were none.

Of the 314 women that made one or more further visits with spine radiographs after baseline, 3 had unevaluable

TABLE 1. BASELINE CHARACTERISTICS FOR 367 SUBJECTS WITH FOLLOW-UP ($n = 367$ UNLESS OTHERWISE STATED)

	Mean (SD) or percentage
Age (yr)	64.6 (9.1)
Height (m)	1.59 (0.063)
Weight (kg)	66.2 (12.3)
BMI (kg/m ²)	26.3 (4.6)
At/near minimum weight ever ($n = 355$)	14%
Fat mass (g) ($n = 363$)	26100 (8970)
TB BMD (g/cm ²) ($n = 366$)	1.069 (0.107)
LS BMD (g/cm ²) ($n = 366$)	1.066 (0.191)
FN BMD (g/cm ²) ($n = 364$)	0.847 (0.136)
Age of menarche	13.4 (1.6)
Age of menopause, if known* ($n = 326$)	48.9 (4.6)
Menarche to menopause (yr)* ($n = 326$)	35.5 (5.0)
Current/ever HRT use	6%/12%
Still premenopausal	4%
Current smoker	20%
No of pack years (if ever smoked) [†]	21.9 (18.2)
Average hand grip strength (mmHg) ($n = 360$)	247 (51)
Carry full suitcase 10 m [‡]	1.6 (0.8)
Stand for one-half hour [‡]	1.6 (0.7)
Run 100 m for bus [‡]	2.3 (0.8)
Daily use of stairs (times up/down) [§]	9.9 (6.1)
Serum calcium (mM) ($n = 359$)	2.38 (0.12)
Serum albumin (g/liter) ($n = 362$)	43.7 (3.2)
Serum total T ₃ (nM) ($n = 357$)	1.95 (0.32)
Serum PTH (pM) ($n = 345$)	4.26 (1.94)
Urine creatinine (μ mol/24 h) ($n = 361$)	7989 (2086)
Urine 24-h output (ml) ($n = 363$)	1652 (529)
Prevalent vertebral fracture ($n = 364$)	7%
Previous nonvertebral fracture	38%

* Either natural or surgical (bilateral oophorectomy), determined retrospectively.

[†] Average cigarettes daily \times number of years smoked/20, $n = 200$.

[‡] Level of difficulty, from 1 (no difficulty) to 3 (unable).

[§] Number of return journeys, excluding 0 (no stairs), for $n = 316$.

films. The vertebral fracture analyses were therefore restricted to 311 subjects. Incident fracture information was available for 98% (nonvertebral fractures) and 83% (vertebral fractures) of the subjects. Almost one half (48.5%) of the original participants attended their 10-yr visit.

During the 10 yr of follow-up, 70 women sustained one or more nonvertebral fractures (81 fractures in all), with a median time to first fracture of 50 mo. The degree of trauma involved could not always be ascertained, and therefore, all confirmed fractures were included regardless of cause. The sites of first nonvertebral fracture, with the number of subjects affected, were as follows: wrist (21), foot or toe (13), hand or finger (8), humerus (7), ankle (6), hip (4), clavicle (4), ribs (3), elbow (2), and pelvis, tibia, and face/skull (1 each). One subject sustained two fractures simultaneously in the same accident. A further 10 fractures were sustained by nine of the subjects: wrist (three), femur (shaft) (two), ribs (two), humerus (one), ankle (one) and hip (one).

At baseline, 25 women had one or more prevalent vertebral fractures, with 40 fractured vertebrae in total, and during the follow-up period, 29 sustained 48 incident ver-

TABLE 2. RISK FACTORS THAT PREDICTED BOTH INCIDENT VERTEBRAL AND NONVERTEBRAL FRACTURES

<i>Risk factor</i>	<i>Nonvertebral fracture [unadjusted RR (95% CI)]</i>	<i>Vertebral fracture [unadjusted RR (95% CI)]</i>
Age (compared with age 50–59)		
60–69 years	1.36 (0.75, 2.46)*	2.17 (0.79, 6.00)*
70–79 years	1.76 (0.91, 3.41)*	4.59 (1.60, 13.1)*
80–85 years	3.81 (1.75, 8.29)*	13.4 (3.51, 51.4)*
BMD (RR per SD decrease)		
Lumbar spine (<i>n</i> = 366)	1.45 (1.12, 1.87) [†]	2.41 (1.57, 3.71)*
Femoral neck (<i>n</i> = 364)	2.09 (1.58, 2.76)*	2.61 (1.70, 4.03)*
Total body (<i>n</i> = 366)	1.84 (1.43, 2.36)*	2.92 (1.90, 4.48)*
Estrogen years (RR per SD decrease) (<i>n</i> = 326)	1.34 (1.06, 1.68) [‡]	1.47 (1.03, 2.11) [‡]
Prevalent vertebral fracture (<i>n</i> = 364)	2.51 (1.24, 5.05) [†]	5.84 (2.49, 13.73)*

* $p \leq 0.001$.[†] $p < 0.01$.[‡] $p < 0.05$.

TABLE 3. RISK FACTORS FOR NONVERTEBRAL FRACTURES ONLY, SHOWING RISK OF VERTEBRAL FRACTURE FOR COMPARISON (AGE-ADJUSTED)

<i>Risk factor</i>	<i>Nonvertebral fractures</i>			<i>Vertebral fractures [age-adjusted RR (95% CI)]</i>
	<i>Unadjusted RR (95% CI)</i>	<i>Adjusted for age</i>	<i>Adjusted for age and FN/LS BMD</i>	
Age at menarche (per 1 yr older)	1.17 (1.02, 1.35)*	NS	NS	
Urine volume (24 h) (per SD decrease)	1.30 (1.02, 1.66)*	NS	NS	
Urinary creatinine (24 h) (per SD decrease)	1.47 (1.18, 1.84) [†]	1.38(1.09,1.75) [†]	NS	1.15 (0.75, 1.74)
PTH (per SD increase, log transformed)	1.36 (1.06, 1.75)*	NS	NS	
Stair use daily, for over 60s (≤ 8 vs. > 8 , median) (<i>n</i> = 190)	2.43 (1.23, 4.79)*	2.43 (1.23, 4.79)*	2.38 (1.20, 4.73)*	1.59 (0.60, 4.20)

* $p < 0.05$.[†] $p < 0.01$.

NS, not significant.

tebral fractures. Seven of the subjects with prevalent fracture(s) also later sustained an incident fracture. The median time to first fracture (date of spine radiograph) was 61 mo.

Risk factors that significantly predicted both nonvertebral and vertebral fractures are shown with relative risks and 95% CIs in Table 2. Older age, lower BMD at all sites, fewer years between menarche and menopause, and presence of prevalent vertebral fracture all predicted both types of fracture (unadjusted). Most lifestyle factors, such as current and previous dietary calcium, alcohol consumption, and sport and exercise history did not predict fractures, and age of menopause (where known) was not a significant predictor for either type of fracture.

There were some factors such as less regular use of stairs in those > 60 yr, low urinary creatinine, low urine volume, high PTH levels, and older age of menarche that predicted nonvertebral fractures only. These are shown, with relative risks and 95% CIs, in Table 3. Frequency of stair use could be an indicator of regular moderate daily activity. Individuals who reported no daily use of stairs were excluded from that particular analysis because of the uncertainty whether their living accommodation reflected greater frailty or disability, and hence inactivity, or not. Urine volume, PTH level and age of menarche lost significance when adjusted for age (in this cohort, there was a trend for later menarche

in the earlier part of the century), whereas the predictive value of urine creatinine and use of stairs was unaffected by age. Although urinary creatinine was significantly related to lean body mass ($r = 0.442$, $p < 0.001$), neither lean mass nor fat mass predicted nonvertebral fractures. Also shown in Table 3 for comparison are the relative risks of vertebral fracture, for each nonvertebral risk factor that was significant when age-adjusted.

When all of the factors that were significant for nonvertebral fracture in univariate analyses, from Tables 2 and 3, were entered into a model without stepwise exclusion (Table 4), only femoral neck BMD remained significant (adjusted RR, 1.99; 95% CI, 1.23, 3.20). Estrogen years (or time between menarche and menopause) had the greatest number of missing values because of the number of premenopausally hysterectomized women with conserved ovaries ($n = 41$). There were 22 values missing for PTH but other variables had only 3% or fewer values missing. Stair use for all subjects was included, not only for those > 60 yr of age. The listwise effect of missing data reduced the number of subjects in the model to 293.

The risk factors that predicted vertebral fractures but did not significantly predict nonvertebral fractures are shown both unadjusted and adjusted for age and BMD in Table 5. They all related to small body size, poor state of health and

TABLE 4. MULTIVARIATE MODEL ($N = 293$) OF ALL INDIVIDUALLY SIGNIFICANT BASELINE RISK FACTORS FOR NONVERTEBRAL FRACTURE, PER SD DECREASE UNLESS OTHERWISE STATED

Risk factor	Multivariate RR (95% CI)	<i>P</i>
Age (per decade increase)	1.03 (0.73, 1.46)	0.86
Lumbar spine BMD	0.70 (0.45, 1.07)	0.10
Femoral neck BMD	1.99 (1.23, 3.20)*	0.005
Total body BMD	1.24 (0.69, 2.22)	0.48
Estrogen years	1.07 (0.79, 1.45)	0.66
Prevalent vertebral fracture	1.26 (0.52, 3.07)	0.61
Age of menarche (per year increase)	1.02 (0.85, 1.23)	0.81
Urine volume	1.11 (0.81, 1.52)	0.51
Urine creatinine	1.17 (0.85, 1.60)	0.33
PTH (per SD increase, log transformed)	1.24 (0.92, 1.68)	0.16
Stair use daily, all ages (≤ 8 vs. > 8 times) [†]	1.24 (0.68, 2.27)	0.48

* $p < 0.01$.

[†] All subjects included.

decreased physical capability. Physical measurements of shorter height, decreased weight (but not decreased body mass index), lower body fat mass, being within 2 kg of minimum adult weight ever, and weaker grip strength predicted vertebral fractures, as did difficulty in carrying out various physical tasks. Greater loss of weight and of fat mass (but not of lean mass) during the study, as annual percentage rates, were associated with incidence of vertebral fractures, and when obese subjects ($BMI > 30 \text{ kg/m}^2$, $n = 57$) were excluded, the association was slightly stronger. The incidence of nonvertebral fractures, on the other hand, seems to be decreased when weight is lost (Table 5). The mean rate of change for weight was $+0.43 \pm 1.60\%$ (SD) and for fat mass was $+0.99 \pm 3.88\%$. Low values of serum albumin, calcium, and total T_3 each predicted vertebral fractures. A history of heavy smoking, defined as the upper quartile of pack years smoked (> 21), tended to be associated with vertebral fractures ($p = 0.061$) and was significant when age and FN BMD were taken into account. Subjects' own assessment of their health status was not significant as a predictor. Table 5 also shows the nonsignificant

TABLE 5. RISK FACTORS FOR VERTEBRAL FRACTURE ONLY: UNADJUSTED AND AGE/BMD-ADJUSTED RELATIVE RISKS PER SD DECREASE, UNLESS OTHERWISE STATED, WITH AGE-ADJUSTED RISK OF NONVERTEBRAL FRACTURE SHOWN FOR COMPARISON

Risk Factor	Vertebral fractures			Nonvertebral fractures [age-adjusted RR (95% CI)]
	Unadjusted RR (95% CI)	Adjusted for age	Adjusted for age and FN/LS BMD	
Height	1.78 (1.23, 2.58)*	NS	NS	
Excluding those with prevalent vertebral fractures	1.68 (1.10, 2.56) [†]			
Weight	1.62 (1.04, 2.54) [†]	1.54 (0.97, 2.44) [§]	NS	1.05 (0.80, 1.37)
Fat mass (g)	1.58 (1.03, 2.43) [†]	1.58 (1.03, 2.44) [†]	NS	1.01 (0.78, 1.30)
Currently at minimum weight ever	2.46 (1.09, 5.56) [†]	2.22 (0.98, 5.02) [¶]	NS	1.06 (0.54, 2.10)
Average grip strength (LQ v rest)	2.85 (1.34, 6.05)*	NS	NS	
Serum calcium	1.70 (1.12, 2.59) [†]	1.50 (0.97, 2.25)**	NS	0.87 (0.71, 1.08)
Serum albumin	2.06 (1.34, 3.16) [‡]	1.76 (1.13, 2.73) [†]	FN: 1.85 (1.20, 2.85)* LS: 1.68 (1.10, 2.59) [†]	1.14 (0.88, 1.48)
Serum total T_3	1.88 (1.34, 2.64) [‡]	1.70 (1.24, 2.32) [‡]	FN: 1.74 (1.26, 2.42) [‡] LS: 1.73 (1.26, 2.37) [‡]	0.98 (0.78, 1.23)
Heavy smoking (UQ vs. nonsmoker)	2.27 (0.96, 5.34) [§]	2.49 (1.04, 5.93) [†]	FN: 2.84 (1.18, 6.81) [†] LS: 2.38 (0.99, 5.72)**	1.48 (0.85, 2.55)
Limited physical ability to ^{††}				
Stand 30 min in a queue	1.77 (1.08, 2.91) [†]	NS	NS	
Carry a full suitcase 10 m	1.90 (1.23, 2.92)*	1.54 (0.99, 2.41) [¶]	NS	0.99 (0.72, 1.36)
Run 100 m for a bus	2.45 (1.36, 4.43)*	1.95 (1.06, 3.59) [†]	FN: 2.21 (1.24, 4.03)* LS: 2.01 (1.09, 3.68) [†]	1.02 (0.74, 1.39)
Weight change (%/yr) nonobese subjects	OR: 1.69 (1.14, 2.50)* OR: 1.90 (1.22, 2.94)*	1.50 (1.00, 2.25) [†] 1.73 (1.09, 2.72) [†]	FN: 1.53 (1.03, 2.29) [†] FN: 1.69 (1.08, 2.65) [†]	0.77 (0.58, 1.03) 0.74 (0.53, 1.05)
Fat mass change (%/yr) nonobese subjects	OR: 1.57 (1.06, 2.35) [†] OR: 1.64 (1.08, 2.49) [†]	NS 1.64 (1.08, 2.49) [†]	NS NS	0.89 (0.66, 1.20) 0.90 (0.66, 1.25)

* $p < 0.01$.

[†] $p < 0.05$.

[‡] $p < 0.001$.

[§] $p < 0.07$.

[¶] $p < 0.06$.

** $p < 0.055$.

^{††} Per self-assessed level of difficulty: 1, without difficulty; 2, can do but with some difficulty; 3, unable to do, or only with help.

NS, not significant.

TABLE 6. MULTIVARIATE MODEL ($N = 241$) OF ALL INDIVIDUALLY SIGNIFICANT BASELINE RISK FACTORS FOR VERTEBRAL FRACTURE, PER SD DECREASE UNLESS OTHERWISE STATED

Risk factor	Multivariate RR (95% CI)	<i>p</i>
Age (per decade increase)	0.88 (0.46, 1.70)	0.71
Lumbar spine BMD	0.64 (0.28, 1.47)	0.29
Femoral neck BMD	1.54 (0.66, 3.60)	0.32
Total body BMD	2.10 (0.76, 5.85)	0.16
Estrogen years*	1.25 (0.75, 2.07)	0.39
Prevalent vertebral fracture	2.75 (0.63, 12.00)	0.18
Height	1.52 (0.86, 2.70)	0.15
Weight	0.15 (0.03, 0.93) [†]	0.043
Fat mass	5.98 (1.06, 33.65) [†]	0.043
Currently at minimum weight	1.77 (0.43, 7.27)	0.43
Grip strength (LQ vs. rest)	1.12 (0.35, 3.56)	0.85
Serum calcium	1.88 (1.00, 3.55) [†]	0.05
Serum albumin	1.15 (0.67, 1.99)	0.61
Serum total T ₃	1.62 (1.09, 2.42) [†]	0.018
Heavy smoking (UQ vs. rest)*	1.75 (0.63, 4.85)	0.28
Per increase in level of difficulty		
Stand 30 min in a queue	0.73 (0.31, 1.74)	0.48
Carry a full suitcase 10 m	0.97 (0.47, 2.00)	0.93
Run 100 m for a bus	2.92 (1.30, 6.57) [‡]	0.010

* All subjects included.

[†] $p \leq 0.05$.

[‡] $p \leq 0.01$.

relative risks and CIs of nonvertebral fracture, for each of these factors that were significant (age-adjusted) for vertebral fracture. Most of the factors gave a nonvertebral fracture risk of close to or less than 1.

When all the baseline factors from Tables 2 and 4 were entered into a model for vertebral fracture without stepwise exclusion (Table 6), six risk factors remained significant as predictors: greater weight, lower fat mass, prevalent vertebral fracture, lower serum calcium, lower serum T₃, and reduced ability to run 100 m for a bus. Missing data reduced the number of subjects in the model to 241.

A weighted risk score was calculated as described in the Materials and Methods section, using the eight risk factors for vertebral fracture that were still significant, or close to significant, when adjusted for age (Table 5). Risk scores could not be calculated for 31 subjects with data missing, such as those unable to recall their minimum weight. The calculated scores ($n = 280$) ranged from 0 to 9, with an increase in fracture risk at higher scores (Fig. 1), rising from a 0% risk (score 0) to a 100% risk (score 9). However, small numbers in the higher risk categories resulted in wide CIs.

To assess the extent to which these factors were a surrogate for the number of comorbidities, we calculated an approximate comorbidity count for each subject as described in the Materials and Methods section, giving values from 0 to 6, and adjusted for age. The age-adjusted comorbidity score was significantly associated with indicators of reduced physical capability such as poor grip strength and limited ability to run for a bus, stand for long periods, or carry a full suitcase. However, there was no association with being at minimum weight, heavy smoking, or albumin or T₃ levels. Body fat mass was significantly correlated with comorbidity

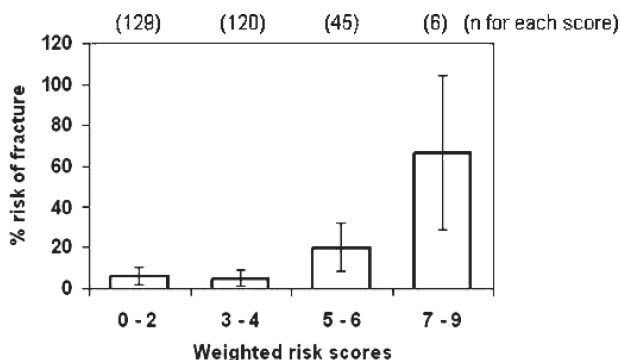


FIG. 1. Percentage risk of incident vertebral fracture by weighted risk score. Risk factors were weighted by multiple regression coefficients as follows: in the lower quartile for body fat mass (0.242), percentage weight change (0.277), serum calcium (1.109), serum albumin (−0.193), serum T₃ (−0.043), in the upper quartile for pack years smoked (0.545), at/near minimum weight (1.140), unable to run for bus (0.965). 95% CIs were calculated for proportions in each risk category ($n = 280$).

score, but positively instead of negatively: those with greater fat mass had more comorbidities.

The rate of change at the lumbar spine was affected by the presence of degenerative changes such as osteoarthritis, endplate sclerosis, and aortic calcification. Approximately 60% of the group had an apparent bone gain at the LS during the study. For these reasons, our analysis examined bone loss at the FN rather than at the LS.

Analysis of bone loss rates was limited to those attending over an interval of at least 5 yr because rates of change in subjects that attended for only two visits, 2 yr apart, were much more variable. The mean annual percentage rate of BMD change at the femoral neck was −0.63% (range, −3.48% to 1.44%, SD 0.73%). Predictors of the rate of change included those shown in Table 7. There were similarities with the predictors of vertebral fracture, relating to poor health, strength, and stamina. Older age, being at minimum weight (but not lower fat mass), weak grip strength, difficulty in carrying out certain physical tasks, a poor self-assessment of health, and lower serum albumin were all predictive of greater bone loss. Although body fat mass and weight at baseline were not related to loss of BMD, a greater rate of loss of weight, fat mass, and lean mass during the study were all associated with loss of FN BMD, independently of age. Loss of fat mass and loss of lean mass were independent of each other in this association.

Furthermore, greater loss at the FN, but not loss at the LS, was associated with incident vertebral fractures independently of age and baseline BMD, with an unadjusted OR of 2.05 per SD decrease in the rate of FN BMD change (95% CI, 1.38, 3.05) or 2.01 (95% CI, 1.34, 3.02) when adjusted for age and FN BMD ($p < 0.001$). When entered into a multiple logistic regression, both the rate of bone loss and the baseline BMD, whether at the FN or LS, contributed a similar magnitude of risk for incident vertebral fracture, as shown in Table 8. The rate of loss was also associated with incident vertebral fracture independently of final BMD at either site.

TABLE 7. FACTORS ASSOCIATED WITH ANNUAL PERCENTAGE FEMORAL NECK BMD CHANGE

<i>Risk factor</i>	<i>Spearman's ρ</i>
Grip strength ($n = 247$)	0.25*
Difficult to stand in queue ($n = 253$)	-0.21*
Run for bus ($n = 253$)	-0.17†
Sit for 1 h ($n = 253$)	-0.14‡
Own health (very good .. poor) ($n = 253$)	-0.15‡
Serum albumin ($n = 249$)	0.25*
Weight change on study (%/yr) ($n = 253$)	0.37*
Fat mass change on study (%/yr) ($n = 253$)	0.29*
Lean mass change on study (%/yr) ($n = 253$)	0.30*
Currently at minimum weight ever ($n = 244$)	Difference -0.34% (<i>t</i> -test)‡

* $p < 0.001$.† $p < 0.01$.‡ $p < 0.05$.TABLE 8. CONTRIBUTIONS TO VERTEBRAL FRACTURE RISK (ORs PER SD DECREASE AND 95% CIs) OF RATE OF FN BMD CHANGE AND BASELINE OR FINAL BMD AT FN OR LS (ALL UNADJUSTED), BY MULTIPLE LOGISTIC REGRESSION ($n = 250$)

<i>BMD site</i>	<i>Baseline BMD</i>	<i>Final BMD</i>	<i>Rate of BMD change</i>
Femoral neck	2.63 (1.52, 4.55)*		2.01 (1.34, 3.02)*
Femoral neck		2.62 (1.45, 4.74)*	1.56 (1.02, 2.39)‡
Lumbar spine	2.38 (1.39, 4.08)†		2.00 (1.34, 3.00)*
Lumbar spine		2.02 (1.21, 3.41)†	1.94 (1.30, 2.91)*

* $p \leq 0.001$.† $p < 0.01$.‡ $p < 0.05$.

The rate of bone loss at the FN was not associated with nonvertebral fractures (OR, 1.13; 95% CI, 0.81, 1.57).

DISCUSSION

Body weight and fat mass

Low body weight predicted vertebral fracture, although weight did correlate with age. However, it was low absolute weight that was significant, not low BMI as in hip fracture.^(12,14) Of overall weight, lean mass was not predictive but fat mass predicted vertebral fracture independently of age.

The association of fat mass with fracture risk is likely to be mediated through BMD and bone loss,⁽²⁴⁻²⁶⁾ and this is supported in our study by the fact that fat mass was not a significant predictor when adjusted for BMD (Table 4). Nevertheless, the multivariate model suggested that, once adjusted for other factors, low fat mass conferred a 6-fold

increased risk of vertebral fracture. Percentage fat mass did not predict fractures, suggesting that a smaller overall body size contributes to the risk. Adipose tissue is the principal source of estrogen in the older woman⁽²⁷⁾ and a source of leptin,⁽²⁶⁾ although Reid et al.⁽²⁸⁾ concluded that its influence on BMD was not explicable in terms of either estrone production or skeletal load bearing. Fat mass has also been found to be an important marker of nutritional status.⁽²⁹⁾

Loss of fat mass conferred a greater risk of vertebral fracture in nonobese subjects, suggesting that a greater baseline body fat mass may be protective. Nevertheless, being at one's lowest weight increased the risk of vertebral fracture independently of weight or fat mass. Although loss of lean mass and of fat mass showed similar associations with BMD change, loss of lean mass was not predictive of vertebral fractures. Ensrud et al.^(30,31) found that weight loss in those >65 yr of age was associated with loss of hip BMD. In our study, the associations were similar in those <65 and >65 yr of age.

Both weight and fat mass were still independently significant factors for vertebral fracture in the multivariate model. However, when the much greater risk conferred by low fat mass was taken into account, a lower overall body weight reduced the risk of fracture.

Height

Short height predicted vertebral fracture even when those with prevalent vertebral fracture were excluded, but not when age was taken into account. It has been found that hip fracture subjects, in contrast, are relatively tall.⁽³²⁻³⁴⁾

Although height at age 25 and age-adjusted current height (excluding prevalent fractures) were slightly shorter in those who had incident fractures, the differences were not significant. However, others have found a shorter arm span and leg length in women who sustain vertebral fractures, suggesting a significantly shorter original height.⁽³⁵⁾

Health and biochemistry results

Low total serum calcium was not a risk factor when adjusted for albumin or age, but nevertheless was significant in the multivariate model, where albumin and age were not. Of the thyroid hormones, only a low total T₃ (and not free T₄, total T₄, or TSH) was predictive of vertebral fracture. Low serum albumin and T₃ were both predictive of fracture independently of age and of each other ($p < 0.01$). Low albumin has been linked to vertebral fracture risk,^(36,37) but not to fractures in general,⁽³⁸⁾ and is known to be associated with ill-health. Similarly, a condition in which T₃ is low (with normal T₄ and TSH) has been described as the "euthyroid sick syndrome" or "nonthyroidal illness syndrome," resulting from ill health, trauma, or malnutrition.⁽³⁹⁾ Low serum T₃ was also one of the significant factors in the multivariate model.

In a large UK study, multiple medical factors increased the risk of vertebral fracture to a significantly greater degree than the risk of hip fracture.⁽⁴⁰⁾ In the Study of Osteoporotic Fractures, a rapid resting heart rate predicted both mortality from all causes and osteoporotic fractures, particularly vertebral fractures.⁽⁴¹⁾ In the same cohort, ver-

tebral fractures were associated with mortality from cancer, cardiovascular disease and many other causes of death. It was suggested that vertebral fractures may be a marker of physiological aging and that in particular, the underlying pathogenesis of vertebral fractures and that of cancer spread may share common factors.⁽¹⁷⁾

Other studies have also found smoking to be associated with bone loss and BMD⁽⁴²⁾ and with vertebral fractures,⁽⁴³⁾ where the increased risk could not be explained by reduced BMD. In our study, the risk from heavy smoking (>21 pack-years) was unaffected by adjusting for BMD. Other results have been inconclusive, however, when the level of smoking was not taken into account.⁽⁴⁴⁾ The effect on fracture risk may be a consequence of an earlier menopause (age of menopause was negatively associated with smoking) or of an effect on general health.

Several significant non-BMD factors, heavy smoking, lower serum albumin, lower serum T₃, and insufficient physical capability to run for a bus were also all individually independent of both LS and FN BMD (Table 5). This suggests that poor health increases vertebral fracture risk by a mechanism other than low BMD. The multivariate model for risk of vertebral fracture did not include any measures of BMD as significant contributory factors.

It would also seem that these frailty measures are not simply a surrogate for comorbidity count. Some risk factors were associated with a comorbidity count and others were not. This is not unexpected, because some comorbidities are related to obesity rather than frailty. The “frailty” risk factors may not present as any specific medical disorder. Poor nutrition, for example, could result in frailty but not necessarily in identifiable comorbidities.

If those in relatively poor health are more at risk for future vertebral fractures, it raises the question of whether the often reported excess in morbidity and mortality after vertebral fracture is simply the long-term consequence of the suboptimal health of those who are most likely to sustain a fracture. In several studies that found excess mortality after vertebral fracture, this lost significance once other indicators of poor health were taken into account.^(45–47) Vertebral fractures may be a result of poor health rather than the other way round. A finding that tends to support this is that vertebral fractures caused by severe trauma do not lead to excess mortality.⁽¹⁹⁾

Physical capability

Most indicators of physical capability such as strength, stamina, and endurance are age related. However, none of these predictors of vertebral fracture in Table 5 were linked to nonvertebral fractures.

In fact, nonvertebral fractures were found in this study to be related inversely to regular, low-intensity activity such as frequency of going up and down stairs. This type of activity was not associated with the incidence of vertebral fractures. Gregg et al.⁽⁴⁸⁾ also found a protective effect of habitual total physical activity against nonvertebral fractures but not vertebral fractures, whereas intensity of activity seemed to protect against vertebral fractures. Weak grip has been found to predict functional decline in vigorous activities⁽⁴⁹⁾

and to be associated with vertebral fractures,⁽⁵⁰⁾ even after adjustment for age and spine BMD.⁽⁵¹⁾ Back extensor strength also showed a negative association with number of vertebral fractures,⁽⁵²⁾ and a randomized intervention trial⁽⁵³⁾ concluded that strengthening back muscles may protect against their incidence. The self-assessed ability to run 100 m for a bus was also significant in the multivariate model. Overall, the results suggest that the risk of vertebral fracture may be related to the strength and stamina required for carrying out certain activities rather than to habitual levels of moderate activity.

Nonvertebral fractures

In this study, nonvertebral fractures at all sites are grouped together. Although fractures at different sites may have some different characteristics and risk factors, virtually all have been found to be related to low BMD.⁽⁵⁴⁾ Increasing age is also a predictor of all fractures. Even so, frailty-related factors did not predict nonvertebral fractures in general. Indeed, being overweight has been identified as a risk for ankle fractures,⁽⁵⁵⁾ and weight loss may even protect against nonvertebral fractures (Table 5). However, some frailty factors may predict certain nonvertebral fractures, such as those of the hip.

Rate of change in BMD

The greater variability of rates of change over only two visits, 2 yr apart, in those subjects not included in the analysis confirms similar observations by He et al.⁽⁵⁶⁾ and Ross et al.⁽⁵⁷⁾

The effects of degenerative changes on rates of bone loss at the LS have also been observed even in younger cohorts, with unexpected results such as an inverse correlation between spine and hip bone loss.⁽⁵⁸⁾ Other studies have found no longitudinal change in LS BMD or have found the rate of change at the spine to be related to severity of osteophytosis.^(59,60)

In a 15-yr study by Riis et al.,⁽⁶¹⁾ incident vertebral fractures were found to be related to significantly greater rates of bone loss but not to lower baseline forearm BMD. Conversely, incidence of Colles' fractures appeared to relate more to low BMD than to rate of loss.

It could be argued, because greater rates of bone loss will generally result in lower BMD eventually, that greater bone loss is simply a surrogate for low BMD around the time of fracture. However, in this study, incident vertebral fractures were significantly associated with higher rates of bone loss independently of not only baseline BMD but also final BMD. “Final” BMD was measured at the last visit made by each subject, at 5, 7, or 10 yr, and therefore postdated the occurrence of any observed vertebral fracture.

The similarities in the risk factors for vertebral fracture and for greater FN bone loss, as well as the equally predictive value of FN BMD (compared with LS BMD) and the relationship between rate of bone loss at the hip and incident vertebral fracture, together suggest that poor physical condition may in some way affect both hip BMD and vertebral propensity to fracture.

Treatment and interventions

Twenty subjects were found during the study to need treatment for osteoporosis or secondary conditions with potential effects on bone. Six of the 20 subjects had medical or surgical treatment for primary hyperparathyroidism, thyrotoxicosis, or Paget's disease. A further eight were treated either for very short periods (2 wk to 5 mo) just before the final visit, only after an incident vertebral fracture, or after leaving the study. Treatment (with hormone replacement therapy or bisphosphonates) of the remaining six, two of whom had an incident vertebral fracture, may have delayed or prevented a fracture.

Conclusions

This study had the advantages of the collection of a wide range of data and a follow-up period of 10 yr, with incident fracture data available for the great majority of subjects. It also had the benefit of a new approach to the diagnosis of vertebral fractures that we believe provides a considerable improvement in accuracy. This has allowed a more reliable distinction to be made between vertebral and nonvertebral fracture risk factors. We have been able to link vertebral fractures prospectively with multiple characteristics of frailty, previously shown only for hip fracture risk.

Limitations included the fact that 20 subjects were found, as described above, to need treatment for osteoporosis or secondary conditions, and these treatments may have reduced the eventual number of incident fractures and therefore weakened the predictive value of some risk factors. Also, those who did not return after the baseline visit, for whom we had no further spine radiographs, were significantly older and therefore more likely to have sustained incident vertebral fractures. The study cohort was not very large, and it is possible that some risk factors for one of the types of fracture may not have been detected. Because of this lack of power, it is felt that the inclusion of some non-significant results may be informative. The cohort is probably also too small to examine threshold effects reliably.

The results suggest that those individuals who are specifically at risk for vertebral fracture are not necessarily those at risk for fractures generally. They seem to be generally smaller, weaker, and less healthy, even adjusting for age, BMD, and other factors, than those who sustain other types of fracture. In multivariate analyses, these other fractures were significantly predicted only by FN BMD, whereas frailty-related factors, and not BMD, were predictors for vertebral fractures. These risk factors also appear to have an additive effect.

In clinical practice, it may be possible to identify those patients who are at considerably increased risk of vertebral fracture, whether or not a BMD measurement or X-ray evidence of a prevalent fracture is available. A combination of factors in an individual gives an even higher risk of fracture. For example in this cohort, a combination of weight in the lower quartile (<58 kg), smoking history in the upper quartile (>21 pack-years), and either a serum albumin or T₃ value in the lower quartile would give an ~5-fold risk of vertebral fracture.

It may also be important, when serial BMD measure-

ments are available, to identify those who lose bone at a faster rate, because these are the patients who seem to be at increased risk of vertebral fracture irrespective of their spine or hip BMD. When BMD is not available, evidence of weight loss over a period in nonobese patients may also indicate a greater risk of vertebral fracture.

ACKNOWLEDGMENTS

We thank the Arthritis Research Campaign for their support in the funding of this study; Caroline Hill for help in study administration and data entry; and the other staff at the Osteoporosis Centre, Northern General Hospital, Sheffield, for contributions to the study over the years.

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Received in original form October 5, 2006; revised form August 28, 2007; accepted August 30, 2007.