0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(3):955–962

doi: 10.1210/jc.2006-1476

Risk Factors for Fracture in Nonosteoporotic Men and Women

Nguyen D. Nguyen, John A. Eisman, Jacqueline R. Center, and Tuan V. Nguyen

Bone and Mineral Research Program (N.D.N., J.A.E., J.R.C., T.V.N.), Garvan Institute of Medical Research, and the Department of Endocrinology (J.A.E., J.R.C.), St. Vincent's Hospital, and the Faculty of Medicine (J.A.E., T.V.N.), The University of New South Wales, Sydney, New South Wales 2010, Australia

Context and Objective: It is not known which factors are associated with fracture in nonosteoporotic elderly. The aim of this study was to assess the association between fall-related risk factors and fracture risk in men and women without osteoporosis.

Design: This study was part of the ongoing Dubbo Osteoporosis Epidemiology Study, which was designed as a prospective population-based cohort investigation.

Participants: At baseline, 924 women and 723 men aged 60+ yr did not have osteoporosis [bone mineral density (BMD) T-scores > -2.5]. The individuals have been followed for up to 15 yr.

Main Outcome Measures: Atraumatic fractures were prospectively identified through radiologists' reports.

Risk Factors: At baseline, femoral neck BMD (FNBMD) was measured by dual energy x-ray absorptiometry (DXA); history of fall, postural stability, and quadriceps strength was obtained.

Results: During the follow-up period, among the nonosteoporotic group, 221 women and 105 men had sustained a fracture, accounting for 55 and 74% of total fractures in the entire Dubbo Osteoporosis Epidemiology Study sample, respectively. The following factors were independent risk factors for any fracture: in women, age per SD (hazard ratio, 1.2; 95% CI, 1.0–1.3), postural sway per SD (1.1, 1.0–1.2), FNBMD per SD (1.6, 1.3–1.9), fall in the previous 12 months (2.1, 1.6–2.7), and prior fracture (1.8, 1.2–2.7); in men, age (1.4, 1.1–1.6), postural sway (1.2, 1.0–1.3), FNBMD (1.2, 1.0–1.5), and fall in the previous 12 months (1.9, 1.2–3.0). Exposure to at least one of the risk factors could account for 49% (women) and 39% (men) of any fractures in this population.

Conclusion: In nonosteoporotic elderly, the combination of low BMD, advancing age, fall during the last 12 months, and prior fracture could identify a subgroup of individuals with high risk of fracture. **(*J Clin Endocrinol Metab* 92: 955–962, 2007)**

ALTHOUGH FRACTURE IS recognized as a multifactorial outcome, previous studies have usually focused on the role of bone mineral density (BMD) in the prediction of risk. This is reasonable because for any given age group, individuals with low BMD have an increased risk of fracture than their counterparts with normal BMD. Indeed, each SD lower BMD is associated with 2- to 3-fold increase in the risk of fracture (1–3). As a result, it has been suggested that individuals with low BMD (*i.e.* BMD T-scores ≤ -2.5) should be treated to reduce their risk of fracture (4, 5). Even in these high-risk individuals, treatment can reduce the risk by around 50% (6).

In recent years, it has been realized that approximately half of all fracture cases occur in individuals without osteoporosis (7). If the aim is to reduce fracture burden in the community, some individuals in this group should also be considered for intervention. However, it is not known which factors are associated with fracture risk in this group. The aim of this study was to estimate the incidence fracture and to assess the association between risk factors and fracture risk in men and women with osteopenia and "normal" BMD.

First Published Online December 12, 2006

Abbreviations: BMD, Bone mineral density; BMI, body mass index; CI, confidence interval; DOES, Dubbo Osteoporosis Epidemiology Study; FNBMD, femoral neck BMD; PARF, population-attributable risk fraction.

Patients and Methods

Study design

Data used in this analysis were derived from the ongoing Dubbo Osteoporosis Epidemiology Study (DOES) for which details of protocol and study design have been previously described (8, 9). The sampling frame for DOES is the city of Dubbo, New South Wales (Australia), a locality of approximately 32,000 people, 98.6% white, of which 1581 men and 2095 women were aged 60 yr or older in 1989. Dubbo had been selected for the study because its age and gender distribution of the population closely resemble the Australian population and its relative isolation in terms of medical care allows virtually complete ascertainment of all fractures. In total, the rate of participation was higher in women (69%) than in men (58%). Among those who agreed to participate in the study, approximately 90% also agreed to have BMD measured. This study was approved by the St. Vincent's Campus Research Ethics Committee and informed written consent was obtained from each participant.

Assessment of risk factors

In addition to anthropometric measurements, each individual was interviewed by a nurse coordinator who administered a structured questionnaire to obtain information on lifestyle and dietary calcium intake. Body weight (kilograms) with light clothing and without shoes was obtained (to the nearest 0.1 kg) on an electronic scale. Standing height (centimeters) without shoes was measured (to the nearest 0.1 cm) by a wall-mounted stadiometer. Lifestyle and clinical data (8–10), any history of falls in the preceding 12 months, and any history of fractures in the past 5 yr were obtained. Information on current and past smoking

habit was obtained from each person that was quantified as the number of pack-years consumed in each 10-yr interval age group.

Dietary calcium intake was assessed based on a food frequency questionnaire as described elsewhere (11). The questionnaire instructed subjects to answer the frequency of consumption of individual food items such as milk and dairy products, eggs, fish, cereals, fruits and vegetables, and others. The total amount of dietary calcium intake then was estimated for each individual nutrient by using a standardized calcium content value.

Physical activity was assessed at baseline as the average number of hours per day spent in each of five levels of activity based on the Framingham Massachusetts Heart Study (12). The five activities were: basal activity (weighting factor 1.0, *e.g.* sleeping, lying down), sedentary (weighting factor 1.1, *e.g.* sitting, standing), light (weighting factor 1.5, *e.g.* casual walking), moderate (weighting factor 2.4, *e.g.* gardening, carpentry), or heavy (weighting factor 5, *e.g.* lifting, digging). The weighting or intensity factor was used based on the approximate oxygen consumption needed for each level of activity (12). The products of hours and weighting factor for all activities were then summed to yield an index of total physical activity per week. High total physical activity index corresponds to lifestyles that are physically active, and low levels correspond to habitual inactivity.

Various risk factors for falling were tested on each subject at baseline. Quadriceps strength (maximum isometric contraction) was measured in the sitting position in the subject's dominant (stronger) leg with a horizontal spring gauge calibrated up to 50 kg force. This method has a reliability coefficient of 0.92 (13). Body sway was measured as displacement of the body at the level of the waist in 30-sec periods. The area (square millimeters) encompassing all movements, forward and backward, left and right, was used as the sway. Four test conditions were used comprising: eyes open and closed on firm surface (wooden floor) and eyes open and closed on compliant surface (high density foam 15-cm high). Full descriptions of these assessments, their test and retest reliability scores, and confidence intervals (CIs) have been given elsewhere (13). The highest value of area of sway obtained was used in the analysis.

BMD (grams per square centimeter) was measured at the lumbar spine and femoral neck by dual energy x-ray absorptiometry using a LUNAR DPX densitometer (GE-LUNAR, Madison, WI). The radiation dose with this method is less than 0.1 μGy. The coefficient of variation of BMD in our institution in normal subjects was 1.5% and 2% at the proximal femur and lumbar spine, respectively (14). Based on the actual values of femoral neck BMD (FNBMD) obtained, each subject was classified as "osteoporotic" with a BMD being 2.5 SD or more below the young normal level or "osteopenic" with a BMD between 2.5 to 1.1 SD below the young normal level or as "normal." The "young normal" BMD was obtained from a sample of 52 Australian men and women aged between 20 to 32 yr. These values are identical to those of LUNAR white database. In this study, individuals with BMD T-scores more than −2.5 were included in the analysis.

Fracture ascertainment

Fractures occurring during the study period were identified for residents of the Dubbo local government area through radiologists' reports from the two centers providing x-ray services as previously described (8, 9). Fractures were only included if the report of fracture was definite and, on interview, had occurred with minimal trauma (fall from standing height or less). Fractures clearly resulting from major trauma (such as motor vehicle accidents) or from underlying diseases (such as cancer or bone-related diseases) were excluded from the analysis. Any fractures more than 3 months before study entry were not considered in the analysis. Fracture was analyzed as any osteoporotic fracture or as subgroups of hip; symptomatic vertebral; wrist and forearm, including Colles', Smith's, and metacarpal fractures; and major fracture, including any osteoporotic fracture, except fracture of the skull, face, fingers, toes, patella, distal tibia ankle, distal tibia, malleus, less than two ribs, and other nonspecified fractures.

Statistical analysis

Incidence of fractures was calculated as fracture cases per 1000 person-yr. Cox's proportional hazards regression model was used to estimate relative risk and 95% CI for each SD change or in specified groups compared with the reference group with categorized risk factors. The outcomes in this model were fracture incidence and the time to fracture from baseline BMD measurement. Stepwise and backward algorithms were used to search for a model with maximum discriminatory power. The significance of parameter estimates derived from the Cox's proportional hazards model (15) was tested with the likelihood ratio statistic (16). The assumption of proportional hazards for the levels of each risk factor was tested by evaluating the linearity of plots of $\log(-\log(S[t_i])_j)$, where $S(t_i)_j$ describes the jth survival time for the ith level (i = 1, 2) for each risk factor. The contribution of risk factors to hip fracture risk was further evaluated in a descriptive analysis in which the measurement of each non-BMD risk factor was dichotomized into two categories (presence or absence). A risk score, or more specifically the number of risk factors, was then derived as the sum of all individual risk factors for each individual. Incidence and relative risk of hip fracture were then computed for each risk score independent of or in combination with BMD values.

To estimate the proportion of fracture that may be hypothetically reduced by the elimination of the risk factors, population-attributable risk fraction (PARF) was calculated. The PARF is a function of two parameters: the prevalence of a risk factor and the relative risk associated with the risk factor. To estimate the prevalence, each of the independent risk factors (obtained from the first stage of analysis) was dichotomized into high-risk and low-risk groups. The relative risk associated with risk of specific fracture types for the high-risk category was then estimated from the multiple logistic model. The statistical estimation of PARF was based on the "sequential attributable fractions" (17). Briefly, for each threshold criterion used to define high-risk individuals, the expected probability of fracture was calculated from the estimated coefficients of the multivariate logistic analysis model. The expected probability was then compared with the observed probability, and components of attributable fraction were subsequently estimated for each possible combination of risk factors.

The PARF can sum to more than one because some individuals with more than one risk factor can have fracture prevented in more than one way and the prevented cases of these individuals could be counted more than once (18). It has been stated that except under special circumstances, PARF estimated the usual way should not be added together (19, 20). To avoid this problem, therefore, we estimated the PARF limits using methods accordingly (18). All database management and statistical analyses were performed with the SAS Statistical Analysis System version 9.1.3 (21).

Results

At baseline, 924 women (or 71.1% of the entire sample) and 723 men (87.5% of the entire sample) were classified as nonosteoporotic. In the entire sample, 395 women (24% of the sample) and 142 men (14%) had sustained at least one fracture during the follow-up period (median, 10 yr for women and 11 yr for men). The number of fractures in the nonosteoporotic sample represents 55% (221 of 395 women) and 74% (105 of 142 men) of total fractures in the DOES cohort (Fig. 1).

Characteristics of nonosteoporotic participants

The overall incidence of fracture (per 1000 person-yr) was 23.1 (95% CI, 15.4–34.6) in women and 14.4 (8.7–24.0) in men. In both sexes, the most common fractures were observed at the vertebrae (27.3% in women and 34.1% in men) followed by the wrist and forearm (25.5% in women and 4.2% in men) and the hip (8.6% in women and 14.4% in men). As expected, there was an inverse relationship between the incidence of fracture and BMD levels (Fig. 2). In both sexes, FNBMD in fracture subjects was approximately 0.4 SD lower than in nonfracture subjects and this difference was more pronounced in those with hip fracture (0.7 SD).

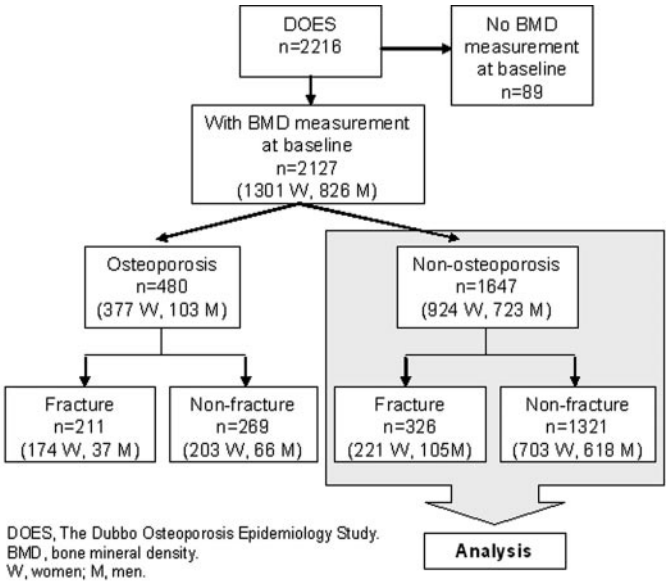

FIG. 1. Data of nonosteoporosis subjects from DOES included in the analysis.

Fractured subjects were older and had significantly higher postural sway and lower quadriceps strength than nonfracture subjects. Fractured subjects also had a greater risk of falling in the previous 12 months compared with those without a fracture. Moreover, subjects with prior fracture had a higher rate of subsequent fracture and the magnitude was more apparently in those with subsequent hip, vertebral, or wrist fractures. There were no differences in terms of weight, height, body mass index (BMI), or lifestyle factors between fracture and nonfracture subjects (Table 1).

Further analysis on those with a fracture stratified by osteoporosis status reveals that in both women and men, osteoporotic individuals were significantly older, had lower weight, BMI, BMD, and quadriceps strength. However, there was no significant difference in dietary calcium intake, physical activity, smoking habit, or fall frequency between the two groups (Table 2).

Independent risk factors of fracture

When all risk factors were simultaneously considered in multivariable Cox's proportional hazards model, the following factors were found to be independent predictors of any fracture risk in both sexes: in women, per SD difference, age (hazard ratio, 1.2; 1.0–1.3), postural instability (1.1, 1.0–1.2), history of fall (2.1, 1.6–2.8), and prior fracture (1.7, 1.2–2.7), and in men, age (1.4, 1.1–1.6), postural instability (1.2, 1.1–1.3), and history of fall (1.9, 1.2–3.0) (Table 3).

Furthermore, the magnitudes of association between each risk factor and fracture risk in the nonosteoporotic sample were comparable to those in the entire DOES sample. For example, in women, each SD lower in FNBMD was associated with an increase in the hazard of fracture by 1.55-fold (95% CI, 1.30–1.85), which was virtually identical to the association observed in the entire DOES sample with a hazard ratio of 1.55 (95% CI, 1.41–1.70).

Further analysis by individual fracture site in both sexes

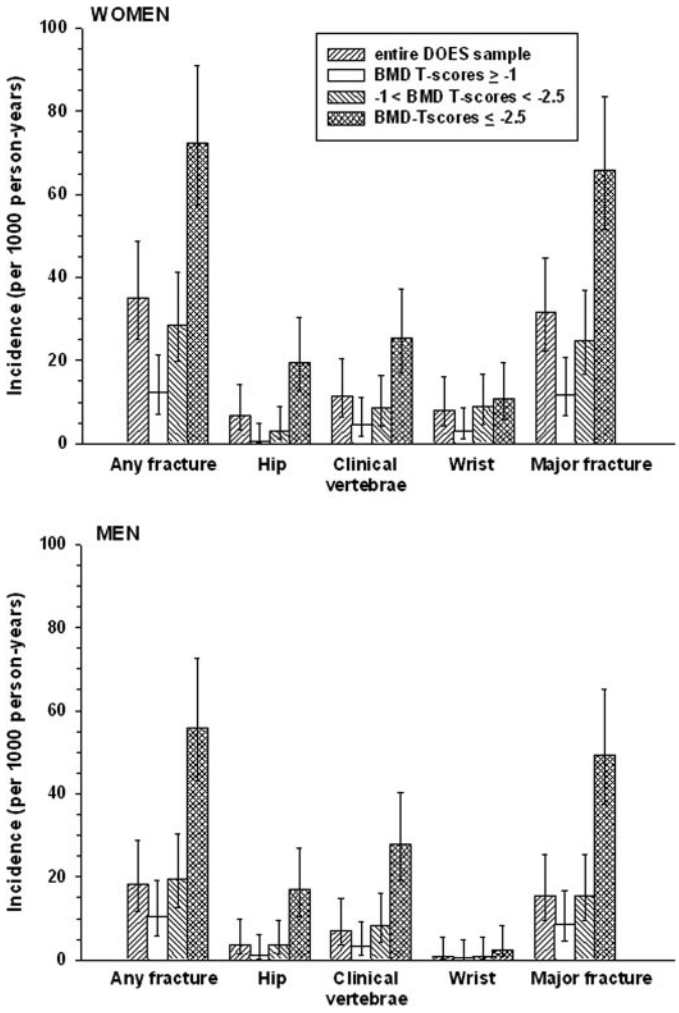

FIG. 2. Incidence of fractures stratified by BMD T-scores for women (*top panel*) and for men (*lower panel*).

indicated that the effect of age, baseline BMD, and prior fracture on the fracture risk were more pronounced on hip, vertebral, and wrist/forearm fractures. In men, however, there was no significant association between baseline BMD and fracture risk at hip and wrist/forearm. Fall was independently associated with any fracture risk in both sexes (Table 4).

Population-attributable risk analysis

To estimate the PARF, each independent continuous risk factor was dichotomized (age $\geq$ 70 yr *vs.* age $<$ 70 yr and osteopenic BMD *vs.* normal BMD), and hazard ratio of fracture was estimated for each and combined factors. Results of the analysis of PARF (Table 5) suggested that in both sexes, the attributable risk fraction generally increased as a function of the cumulative presence of risk factors and the incidence of fracture of the corresponding risk factors. In this sample, 68.5% in women and 46.2% in men had osteopenia ($-2.5 <$ BMD T-score < -1.0), 39.9% women and 45.5% men were 70 yr of age or older, 25.0% women and 17.3% men had a history of fall in the last 12 months, and 10.2% women and 8.4% men had fractures in the last 5 yr. Approximately 82% of women

TABLE 1. Characteristics of nonosteoporotic participants at study entry

Variable	Nonfracture	Any fracture[c]	Hip[d]	Clinical vertebrae[e]	Wrist/forearm[f]	Major fractures[g]
Women	(n = 703)	(n = 221)	(n = 24)	(n = 76)	(n = 71)	(n = 199)
Age (yr)	68.7 ± 6.3	70.0 ± 6.4[h]	73.3 ± 6.8[i]	70.8 ± 5.9[i]	69.5 ± 6.4	69.9 ± 6.5
Weight (kg)	68.4 ± 12.2	67.9 ± 11.0	67.7 ± 10.6	66.9 ± 10.9	67.2 ± 10.2	68 ± 11.1
Height (cm)	160.7 ± 5.8	161.2 ± 6.1	160.8 ± 6.7	160.7 ± 6.3	161.2 ± 6.0	160.8 ± 6.2
BMI (kg/m^2)	26.5 ± 4.7	26.1 ± 4.4	26.3 ± 4.6	25.9 ± 3.9	26.0 ± 4.2	26.3 ± 4.4
FNBMD (g/cm^2)	0.85 ± 0.10	0.81 ± 0.08[i]	0.77 ± 0.05[i]	0.81 ± 0.08[i]	0.80 ± 0.07[i]	0.81 ± 0.08[i]
LSBMD (g/cm^2)	1.09 ± 0.18	1.02 ± 0.17[i]	1.09 ± 0.17	1 ± 0.17[i]	0.97 ± 0.17[i]	1.01 ± 0.17[i]
Postural sway (cm^2)[a]	11 (7, 18)	12 (7, 24)[h]	14 (8, 37)	11 (7, 21)	11 (6, 19)	11 (7, 21)
Quadriceps strength (kg)[a]	20 (16, 26)	19 (14, 24)	14 (10, 19)[i]	20 (16, 24)	19 (14, 24)	19 (14, 24)
Calcium intake (mg/d)[a]	583 (424, 808)	555 (398, 803)	489 (312, 807)	559 (387, 791)	552 (387, 830)	560 (402, 801)
Physical activity (METs)[a]	78 (62, 101)	77 (59, 102)	90 (76, 109)	75 (61, 103)	72 (56, 93)	78 (62, 105)
Fall during the last 12 months[b]	146 (20.8)	85 (38.5)[i]	10 (41.7)[i]	23 (30.3)[i]	25 (35.2)[i]	75 (37.6)[i]
Prior fracture[b]	48 (6.8)	28 (12.7)[i]	6 (25)[h]	22 (29)[i]	25 (35.2)[i]	28 (14.1)[i]
Current/ex-smokers[b]	197 (28.0)	61 (27.6)	5 (20.8)	23 (30.3)	25 (35.2)	57 (28.6)
Menopause age	46.9 ± 6.9	47 ± 6.6	45.5 ± 7.9	46.6 ± 6.7	46.2 ± 7.1	46.9 ± 6.7
Men	(n = 618)	(n = 105)	(n = 17)	(n = 41)	(n = 5)	(n = 86)
Age (yr)	69.3 ± 5.9	72.2 ± 6.3[i]	76.1 ± 7.0[i]	72.2 ± 5.2[i]	68.6 ± 6.6	72.2 ± 6.3
Weight (kg)	80.0 ± 12.4	77.5 ± 11.0	78.6 ± 11.3	74.1 ± 10.0[i]	86.8 ± 8.5	78.3 ± 11.4
Height (cm)	174.0 ± 6.7	172.8 ± 6.8	173.5 ± 7.7	171.7 ± 5.7[i]	174.6 ± 6.5	172.8 ± 6.9
BMI (kg/m^2)	26.4 ± 3.6	25.9 ± 3.2	26.0 ± 2.6	25.0 ± 3.1[i]	28.6 ± 3.2	25.9 ± 3.2
FNBMD (g/cm^2)	0.95 ± 0.13	0.90.11[i]	0.870.11[i]	0.88 ± 0.08[i]	0.97 ± 0.17	0.9 ± 0.11
LSBMD (g/cm^2)	1.28 ± 0.20	1.22 ± 0.20[i]	1.26 ± 0.15	1.17 ± 0.21[i]	1.3 ± 0.22	1.22 ± 0.20
Postural sway (cm^2)[a]	10 (7, 16)	15 (9.30)[i]	15 (6, 145)[i]	16 (10, 66)[i]	14 (7, 40)	14 (9, 30)
Quadriceps strength (kg)[a]	36 (28, 44)	32 (24, 43)[h]	26 (22, 32)[i]	27 (21, 36)[i]	44 (40, 49)	44 (40, 49)
Calcium intake (mg/d)[a]	599 (419, 805)	541 (399, 814)	520 (343, 795)	592 401, 794)	549 (381, 839)	541 (376, 807)
Physical activity (METs)[a]	66 (40, 102)	66 (36, 111)	62 (43, 95)	54 (36, 119)	91 (54, 114)	63 (36, 110)
Fall during the last 12 months[b]	96 (15.5)	29 (27.6)	5 (29.4)	10 (24.4)[i]	1 (20.0)	25 (29.1)
Prior fracture[b]	37 (6.0)	11 (10.5)	5 (29.4)[i]	8 (19.5)[i]	0	14 (16.3)[h]
Current/ex-smokers[b]	366 (59.2)	65 (61.9)	9 (52.9)	33 (80.5)	2 (40.0)	53 (61.6)

Values are mean ± SD (unpaired *t* test) or as otherwise specified. LSBMD, Lumbar spine BMD; METs, metabolic equivalents.
[a] Median (interquartile range, Q1, Q3), Mann-Whitney *U* test.
[b] Number (percentage), χ^2 test.
[c,d,e,f,g] Statistically significant difference between fracture and nonfracture groups is indicated.
[h] $P < 0.05$ to 0.01.
[i] $P < 0.001$.

and 73% of men had at least one risk factor, 38% women and 47% men had at least two risk factors, 13% women and 8% men had at least three risk factors, and 1% had four risk factors in both sexes.

The PARF for each combination of risk factors varied according to fracture site. For example, in women, the PARF of the combination of the presence of four risk factors (*i.e.* the presence of age ≥ 70 yr, osteopenic BMD, history of fall and fracture) were approximately 2, 15, and 9% for any fracture, hip fracture, and vertebral fracture, respectively. However, in women, the major contribution to PARFs was osteopenia. Indeed, in women, osteopenia and fall were the two most

TABLE 2. Baseline characteristics of subjects with fracture stratified by osteoporotic status

Variable	Women		Men	
	Nonosteoporosis	Osteoporosis	Nonosteoporosis	Osteoporosis
Age (yr)	70.0 ± 6.4	74.9 ± 7.9[d]	72.2 ± 6.3	76.0 ± 7.8[d]
Weight (kg)	67.9 ± 11.0	56.6 ± 9.9[d]	77.5 ± 11.0	66.2 ± 12.7[d]
Height (cm)	161.2 ± 6.1	156.4 ± 6.6[d]	172.8 ± 6.8	167.1 ± 5.1[d]
BMI (kg/m^2)	26.1 ± 4.4	23.1 ± 3.7[d]	25.9 ± 3.2	23.6 ± 4.4[d]
FNBMD (g/cm^2)	0.81 ± 0.08	0.62 ± 0.07[d]	0.90 ± 0.11	0.63 ± 0.10[d]
LSBMD (g/cm^2)	1.02 ± 0.17	0.88 ± 0.16[d]	1.22 ± 0.20	1.01 ± 0.17[d]
Postural sway (cm^2)[a]	12 (7, 24)	16 (9, 148)	15 (9, 30)	22 (7, 148)[d]
Quadriceps strength (kg)[a]	19 (14, 24)	16 (12, 20)[d]	32 (24, 43)	25 (18, 32)[d]
Calcium intake (mg/d)[a]	555 (398, 803)	609 (405, 811)	541 (399, 814)	515 (282, 824)
Physical activity (METs)[a]	77 (59, 102)	77 (60, 104)	66 (36, 111)	90 (79, 101)
Fall during the last 12 months[b]	85 (38.5)	69 (39.7)	29 (27.6)	12 (32.4)
Prior fracture[b]	28 (12.7)	20 (11.5)[c]	11 (10.5)	9 (24.3)
Current/ex-smokers[b]	61 (27.6)	63 (36.2)	65 (61.9)	26 (70.3)
Menopause age	47.0 ± 6.6	45.6 ± 7.5		

Values are mean ± standard deviation (unpaired *t* test) or otherwise specified. LSBMD, Lumbar spine BMD; METs, metabolic equivalents.
[a] Median (interquartile range, Q1, Q3), Mann-Whitney *U* test.
[b] Number (percentage), χ^2 test.
Statistically significant difference between osteoporosis and nonosteoporosis is indicated by [c] $P < 0.05$ or [d] $P < 0.001$.

TABLE 3. Independent predictors for any fracture risk in the entire sample and in osteoporotic and nonosteoporotic groups (multivariate)

	Unit of comparison	Nonosteoporotic sample	Entire DOES sample
Women			
Age	+5 yr	1.15 (1.03–1.28)	1.09 (1.01–1.18)
Postural sway	+40 cm^2	1.11 (1.01–1.22)	1.08 (1.02–1.15)
FNBMD	−0.12 g/cm^2	1.55 (1.30–1.85)	1.55 (1.41–1.70)
Fall during the last 12 months	Yes	2.05 (1.55–2.72)	1.89 (1.52–2.34)
Prior fracture	Yes	1.76 (1.17–2.65)	
Men			
Age	+5 yr	1.35 (1.14–1.61)	1.33 (1.16–1.54)
Postural sway	+40 cm^2	1.15 (1.00–1.31)	1.13 (1.02–1.25)
FNBMD	−0.12 g/cm^2	1.22 (1.02–1.46)	1.39 (1.22–1.59)
Fall during the last 12 months	Yes	1.87 (1.19–2.95)	1.79 (1.21–2.63)
Prior fracture	Yes		

Values are hazard ratios (95% CI). Variables included in the model: age, postural sway, quadriceps strength, FNBMD, fall, and prior fracture. The model was tested by using multivariate Cox's proportional hazards model with backward elimination algorithm.

important risk factors for any fracture and the major after adjustment for the other factors, whereas osteopenia and prior fracture played the most important role for the fracture risk at hip and vertebral. In this study sample, if osteopenia were eliminated and all other risk factors were unchanged, 32 to 40% of any fracture cases in women and 13 to 20% in men would be prevented; the figures were less pronounced for the elimination of fall (11–17% in women and 6–10% in men), age (4–7% in women and 19–26% in men), and prior fracture (2–4% for both sexes) risk factors.

Discussion

Although it is recognized that the majority of women who fracture do not have low BMD (*i.e.* osteoporosis) (22–28), it is not known which risk factors contribute to the fracture risk in this nonosteoporotic group. The present study's results suggest that apart from advancing age, low BMD, fall and fall-related factors, and prior fracture account for a substantial proportion of fractures in this group. The attribution to BMD in women was higher than in men despite the magnitude of BMD–fracture association being the same for men and women. This is because the prevalence of osteopenia in women (69%) was higher than that in men (46%). Thus, in these nonosteoporotic individuals, BMD is still the best predictor of fracture risk.

As expected, the incidence rates of fracture among nonosteoporotic women and men were lower than their counterparts in the general population and particularly lower than those with osteoporotic BMD. Although the incidence rate of any osteoporotic fracture in women was 1.6-fold higher than that in men, the incidence rate of hip fracture was the same in nonosteoporotic women and men (2.2 per 1000 person-yr). This is lower than a previous report of the incidence among nonosteoporotic women was 4.1 person-per 1000 yr (29). The discrepancy for this could be the result of the age difference. The average age among fractured women in this study was 70 yr *vs.* 77 yr in the other report, and it is recognized that incidence of fracture increases with advancing age independently of BMD. In the present study, the incidence of wrist and forearm fracture was much higher in women compared with that in men (relative risk = 10.5; 95% CI, 4.3–26.1).

The magnitude of the association between BMD and fracture in nonosteoporotic women was comparable to that in the entire sample and in general white women population (3) in which each SD decrease in BMD is associated with approx-

TABLE 4. Independent predictors of fracture risk at specific site in women and men without osteoporosis at the femoral neck

	Unit of comparison	Hip		Clinical vertebrae		Wrist/forearm		Major fracture	
Women									
Age	+5 yr	**1.6**	**(1.1–2.2)**	**1.3**	**(1.1–1.6)**	**1.3**	**(1.0–1.6)**	**1.1**	**(1.0–1.3)**
Postural sway	+40 cm^2							**1.1**	**(1.0–1.2)**
Quadriceps strength	−10 kg	**1.7**	**(1.1–2.7)**						
FNBMD	−0.12 g/cm^2	**3.7**	**(1.6–8.4)**	**1.5**	**(1.1–2.1)**	**1.9**	**(1.3–2.6)**	**1.6**	**(1.3–1.9)**
Fall during the last 12 months	Yes	**2.6**	**(1.0–6.3)**	*1.5*	*(0.7–3.2)*	**1.9**	**(1.1–3.1)**	**2.0**	**(1.5–2.7)**
Prior fracture	Yes	**4.1**	**(1.5–11.5)**	**5.2**	**(3.1–8.8)**	**5.8**	**(3.5–9.7)**	**1.9**	**(1.3–2.9)**
Men									
Age	+5 yr	**2.6**	**(1.7–3.9)**	**1.3**	**(1.0–1.8)**			**1.4**	**(1.1–1.7)**
Postural sway	+40 cm^2							**1.2**	**(1.0–1.4)**
Quadriceps strength	−10 kg			**1.4**	**(1.1–1.7)**				
FNBMD	−0.12 g/cm^2	*1.4*	*(0.8–2.3)*	**1.6**	**(1.1–2.2)**				
Fall during the last 12 months	Yes							**2.1**	**(1.3–3.4)**
Prior fracture	Yes	**7.5**	**(2.2–25.3)**	**3.9**	**(1.8–8.7)**			**2.9**	**(1.6–5.3)**

Values are hazard ratios (95% CI); statistically significant values are shown in *bold*, and risk factors that showed the trend of association but did not reach a statistically significant level are shown in *italics*. Models included all statistically significant risk factors in univariate analysis and were tested by using multivariate Cox's proportional hazards model with backward elimination algorithm. Major fractures included any osteoporotic fracture, except fracture of the skull, face, fingers, toes, patella, distal tibia ankle, distal tibia, malleus, less than two ribs, and other nonspecified fractures.

TABLE 5. PARF estimates for combinations of risk factors age, FNBMD, and fall or prior fracture in women and men without osteoporosis at the femoral neck

Risk factors				Any fracture		Hip fracture		Vertebral fracture		Wrist/forearm fracture		Major fracture	
1	2	3	4	P	PARF	P	PARF	P	PARF	P	PARF	P	PARF
Women													
−	−	−	−	17.7	0.0	18.1	0.0	17.7	0.0	18.0	0.0	17.7	0.0
−	−	−	+	0.6	0.2	0.5	0.2	0.5	0.8	0.6	1.0	0.6	0.2
−	−	+	−	3.7	1.6	3.6	0.8	3.8	0.8	3.6	1.3	3.7	1.6
−	−	+	+	0.3	0.3	0.2	0.2	0.3	0.7	0.2	0.7	0.3	0.3
−	+	−	−	27.2	12.7	27.2	17.2	27.1	10.9	27.1	15.4	27.2	12.5
−	+	−	+	1.8	1.7	2.5	5.8	2.5	7.0	3.0	11.8	2.1	2.2
−	+	+	−	7.4	8.8	7.0	12.9	6.9	5.5	6.3	9.3	6.9	8.0
−	+	+	+	1.3	2.3	1.0	5.6	1.2	4.6	1.3	8.2	1.5	2.9
+	−	−	−	5.0	0.4	4.9	0.8	4.8	0.9	4.9	0.1	4.9	0.4
+	−	−	+	0.5	0.2	0.8	0.6	0.8	1.6	0.8	1.2	0.6	0.3
+	−	+	−	3.4	2.0	3.4	2.1	3.5	1.7	3.4	1.3	3.5	2.0
+	−	+	+	0.2	0.2	0.1	0.3	0.1	0.3	0.1	0.4	0.1	0.1
+	+	−	−	19.6	12.3	18.9	27.0	19.2	14.0	18.6	11.3	19.5	11.6
+	+	−	+	2.5	2.7	3.7	17.0	3.2	12.0	3.8	15.2	2.6	3.3
+	+	+	−	7.9	11.2	6.8	25.5	6.5	8.1	6.8	10.6	7.9	10.7
+	+	+	+	0.9	1.7	1.4	14.5	1.9	9.4	1.6	10.5	0.9	1.9
Men													
−	−	−	−	26.7	0.0	27.1	0.0	26.8	0.0	−	−	20.9	0.0
−	−	−	+	1.1	0.3	1.2	1.1	1.4	0.8	−	−	1.0	0.8
−	−	+	−	3.9	1.3	3.2	0.4	3.5	0.8	−	−	2.9	1.6
−	−	+	+	0.7	0.5	0.8	1.2	0.7	0.7	−	−	0.5	1.0
−	+	−	−	18.5	5.4	18.4	6.1	18.1	10.9	−	−	14.3	4.6
−	+	−	+	1.1	0.7	0.8	1.9	1.1	7.0	−	−	1.0	1.4
−	+	+	−	2.5	2.0	2.8	1.7	2.9	5.5	−	−	2.1	2.2
−	+	+	+	0.0	0.0	0.1	0.5	0.0	4.6	−	−	0.0	0.0
+	−	−	−	16.9	6.8	16.0	9.2	16.3	0.9	−	−	12.9	6.1
+	−	−	+	0.8	0.6	1.2	4.1	1.4	1.6	−	−	0.8	1.3
+	−	+	−	3.5	3.3	3.7	3.5	3.3	1.7	−	−	2.7	3.6
+	−	+	+	0.3	0.4	0.4	2.0	0.4	0.3	−	−	0.4	1.4
+	+	−	−	16.0	14.0	15.5	24.8	15.4	14.0	−	−	12.1	12.0
+	+	−	+	1.5	2.1	2.1	14.6	2.2	12.0	−	−	1.5	4.0
+	+	+	−	5.4	8.7	4.8	11.6	5.4	8.1	−	−	4.3	9.2
+	+	+	+	1.1	2.5	1.7	16.0	1.1	9.4	−	−	0.9	3.7

Values are percentages. P, Prevalence of the combination of risk factors. Risk factors: 1, age 70 yr or older; 2, osteopenia, −2.5 less than BMD T-scores less than −1.0; 3, fall in the last 12 months; 4, prior fracture; (−), risk absence, and (+), risk presence. Major fractures included any osteoporotic fracture, except fracture of the skull, face, fingers, toes, patella, distal tibia ankle, distal tibia, malleus, less than two ribs, and other nonspecified fractures. PARF of wrist/forearm fracture was not calculated for men.

imately 50% increase in fracture risk. The present study also showed that, in both sexes, in predicting hip fracture risk, FNBMD had better predictive value than lumbar spine BMD. This finding is consistent with previous Dubbo and meta-analysis data (3, 30). However, both measurements at the femoral neck and lumbar spine had similar predictive values for vertebral and other fractures.

These data suggest the concept that fracture prevention should be expanded beyond BMD to include fall prevention as a primary component, because at least 12% of fracture cases in women could be attributed to falls. However, this figure is less in men (6%), which might be the result of a lower prevalence of prior fall among men without osteoporosis (17 *vs.* 25% in women). The association between falls and fracture risk may be mediated by vitamin D deficiency and high PTH. Muscle weakness, a predictor of fall and fracture, has been shown to be associated with long-term vitamin D deficiency (31, 32). Moreover, hyperparathyroidism is associated with motor neuron impairment (33). The present study did not measure serum calcium, vitamin D, and PTH levels for all participants; therefore, it was not possible to analyze the association between these hormones and fracture risk. Nevertheless, a previous analysis of data from a subsample of men in DOES found that fracture risk was significantly associated with reduced 25(OH)D but not with PTH (34), and none of the men in the study sample had vitamin D deficiency status.

The finding that postural sway was an independent predictor of any fracture is consistent with previous observation in the general population (8). The association between postural sway and quadriceps weakness and fracture is presumably mediated by falls, because increased body sway as a measure of postural instability (35, 36) is a predictor of falls (37) along with impaired tactile sensitivity, joint position sense, and reaction time alone (13).

The present results also confirmed that prior fracture was a predictor of subsequent fracture (38, 39). It is noted that the magnitude of the prior fracture–fracture risk relationship in men was comparable to that in women. It seems prior fracture had a "stringent" effect on subsequent fracture in men than in women. The magnitude of association between prior fracture and subsequent fracture were more pronounced at specific sites such as hip, vertebrae, and wrist fracture. This is because incident hip and vertebral fractures in this study

were the secondary fractures rather than primarily incident events. The relation between prior fracture and hip fracture among nonosteoporotic women in the present study is consistent with that of previous study (40). However, only 4% (women) and 7% (men) of incident hip fractures in nonosteoporotic subjects were attributable to prior fracture. The corresponding rates were more pronounced in vertebral (14%) and wrist/forearm (16%) fractures in women compared with 6% in vertebral in men.

In the general population, the incidence of fracture increases with advancing age (8, 41–43). Although the present study showed that the effect of age on fracture risk in women without osteoporosis was independent of BMD, the magnitude of effect was modest. Only 4 to 7% of fracture cases in nonosteoporotic women could be attributed to advancing age *per se*. This is because among those who fractured, approximately half were aged 70+ yr, and in this group, the magnitude of the association between advancing age and fracture was modest (hazard ratio = 1.3). However, the effect of age on fracture risk was greater in men with a PARF at least 20% of fracture cases.

The existence of the other independent risk factors for fracture in women and men without osteoporosis cannot be ruled out, because approximately half of women and two thirds of men who experienced fracture were not "explained" by the combination of osteopenia, advancing age, fall, and prior fracture. However, additional risk factors would have to be sufficiently prevalent and strongly related to fracture to make a substantial contribution to the fracture incidence in the general population. In the present study, lifestyle factors such as calcium intake, physical activity, and smoking status were not found to have any association with fracture risk among nonosteoporotic women and men.

This prospective study overcomes several biases inherent in cross-sectional or case-control studies of the association between BMD and other risk factors and fractures. The study was based on a relatively large sample size with long duration of follow up. Furthermore, participants in this study were essentially volunteers and were generally healthier than those who did not participate (44). Therefore, the magnitude of association between risk factors and fracture risk could have been underestimated.

The findings from the present study have important implications in clinical practice. Currently, treatment is recommended for individuals with low BMD (*i.e.* BMD T-scores ≤ -2.5) to reduce their risk of fracture (4, 5). BMD T-scores have also been used as criterion to recruit participants for intervention trials. The findings from this study confirm that the BMD-fracture risk relationship is a continuous one. That means there is no arbitrary cutoff value that can better discriminate fracture subjects from nonfracture counterparts. Therefore, the criteria for treatment recommendation and for recruitment of trials could perhaps better be based on individual absolute risk rather than any cutoff BMD value.

In conclusion, postural instability, quadriceps weakness, and history of fall or prior fracture were significant predictors of subsequent osteoporotic fractures independent of baseline BMD and age in women and men without osteoporosis. The combination of those predictors could identify a subgroup of women and men who were not osteoporotic but at high risk of fractures. Selecting patients for intervention to reduce the community burden of fractures, therefore, should be not only based on BMD values and interventions should arguably be focused on the contributory risk factors.

Acknowledgments

We gratefully acknowledge the assistance of Sr. Janet Watters and Donna Reeves for the interview, data collection, and BMD measurement. We also appreciate the invaluable help of the staff of Dubbo Base Hospital. We thank Natasa Ivankovic and Jim McBride for the management of the database.

Received July 11, 2006. Accepted December 1, 2006.

Address all correspondence and requests for reprints to: Tuan V. Nguyen, Bone and Mineral Research Program, Garvan Institute of Medical Research, St. Vincent's Hospital, 384 Victoria Street, Darlinghurst, Sydney, New South Wales 2010, Australia. E-mail: t.nguyen@garvan.org.au.

This work has been supported by the National Health and Medical Research Council of Australia and untied educational grants from GE-Lunar, Merck Australia, Eli Lilly International, and Aventis Australia. N.D.N. is a recipient of a Postgraduate Research Award from the National Health and Medical Research Council of Australia.

Disclosure Statement: The authors have nothing to disclose.

References

1. **Nguyen TV, Livshits G, Center JR, Yakovenko K, Eisman JA** 2003 Genetic determination of bone mineral density: evidence for a major gene. J Clin Endocrinol Metab 88:3614–3620
2. **Melton Jr L, Atkinson EJ, O'Fallon WM, Wahner HW, Riggs BL** 1993 Long-term fracture prediction by bone mineral assessed at different skeletal sites. J Bone Miner Res 8:1227–1233
3. **Marshall D, Johnell O, Wedel H** 1996 Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 312: 1254–1259
4. **Sambrook PN, Seeman E, Phillips SR, Ebeling PR** 2002 Preventing osteoporosis: outcomes of the Australian Fracture Prevention Summit. Med J Aust 176(Suppl):S1–S16
5. **Brown JP, Josse RG** 2002 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 167:S1–S34
6. **Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C** 2002 Meta-analyses of therapies for postmenopausal osteoporosis. IX: summary of meta-analyses of therapies for postmenopausal osteoporosis. Endocr Rev 23:570–578
7. **World Health Organization** 1994 Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Technical Report Series 843. Geneva: World Health Organization
8. **Nguyen T, Sambrook P, Kelly P, Jones G, Lord S, Freund J, Eisman J** 1993 Prediction of osteoporotic fractures by postural instability and bone density. BMJ 307:1111–1115
9. **Jones G, Nguyen T, Sambrook PN, Kelly PJ, Gilbert C, Eisman JA** 1994 Symptomatic fracture incidence in elderly men and women: the Dubbo Osteoporosis Epidemiology Study (DOES). Osteoporos Int 4:277–282
10. **Nguyen TV, Kelly PJ, Sambrook PN, Gilbert C, Pocock NA, Eisman JA** 1994 Lifestyle factors and bone density in the elderly: implications for osteoporosis prevention. J Bone Miner Res 9:1339–1346
11. **Angus RM, Sambrook PN, Pocock NA, Eisman JA** 1989 A simple method for assessing calcium intake in Caucasian women. J Am Diet Assoc 89:209–214
12. **Kannel WB, Sorlie P** 1979 Some health benefits of physical activity. The Framingham Study. Arch Intern Med 139:857–861
13. **Lord SR, Clark RD, Webster IW** 1991 Postural stability and associated physiological factors in a population of aged persons. J Gerontol 46:M69–M76
14. **Nguyen TV, Sambrook PN, Eisman JA** 1997 Sources of variability in bone mineral density measurements: implications for study design and analysis of bone loss. J Bone Miner Res 12:124–135
15. **Cox DR** 1972 Regression models and life tables. J R Stat Soc (B) 34:187–220
16. **Lee ET** 1980 Statistical models for survival data analysis. Belmont, CA: Lifetime Learning Publications
17. **Eide GE, Gefeller O** 1995 Sequential and average attributable fractions as aids in the selection of preventive strategies. J Clin Epidemiol 48:645–655
18. **Rowe AK, Powell KE, Flanders WD** 2004 Why population attributable fractions can sum to more than one. Am J Prev Med 26:243–249
19. **Rockhill B, Newman B, Weinberg C** 1998 Use and misuse of population attributable fractions. Am J Public Health 88:15–19
20. **Walter SD** 1983 Effects of interaction, confounding and observational error on attributable risk estimation. Am J Epidemiol 117:598–604

21. **SAS Institute Inc.** 2004 Base SAS 9.1.3 procedures guide. Vol 1–4. 9.1.3 (TS1M3) ed. Cary, NC: SAS Publishing
22. **Karlsson MK, Johnell O, Nilsson BE, Sernbo I, Obrant KJ** 1993 Bone mineral mass in hip fracture patients. Bone 14:161–165
23. **Earnshaw SA, Cawte SA, Worley A, Hosking DJ** 1998 Colles' fracture of the wrist as an indicator of underlying osteoporosis in postmenopausal women: a prospective study of bone mineral density and bone turnover rate. Osteoporos Int 8:53–60
24. **Black DM, Steinbuch M, Palermo L, Dargent-Molina P, Lindsay R, Hoseyni MS, Johnell O** 2001 An assessment tool for predicting fracture risk in postmenopausal women. Osteoporos Int 12:519–528
25. **Schott AM, Cormier C, Hans D, Favier F, Hausherr E, Dargent-Molina P, Delmas PD, Ribot C, Sebert JL, Breart G, Meunier PJ** 1998 How hip and whole-body bone mineral density predict hip fracture in elderly women: the EPIDOS Prospective Study. Osteoporos Int 8:247–254
26. **Stone KL, Seeley DG, Lui LY, Cauley JA, Ensrud K, Browner WS, Nevitt MC, Cummings SR** 2003 BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. J Bone Miner Res 18:1947–1954
27. **Miller PD, Barlas S, Brenneman SK, Abbott TA, Chen YT, Barrett-Connor E, Siris ES** 2004 An approach to identifying osteopenic women at increased short-term risk of fracture. Arch Intern Med 164:1113–1120
28. **Siris ES, Chen YT, Abbott TA, Barrett-Connor E, Miller PD, Wehren LE, Berger ML** 2004 Bone mineral density thresholds for pharmacological intervention to prevent fractures. Arch Intern Med 164:1108–1112
29. **Wainwright SA, Marshall LM, Ensrud KE, Cauley JA, Black DM, Hillier TA, Hochberg MC, Vogt MT, Orwoll ES** 2005 Hip fracture in women without osteoporosis. J Clin Endocrinol Metab 90:2787–2793
30. **Nguyen TV, Center JR, Eisman JA** 2004 Bone mineral density-independent association of quantitative ultrasound measurements and fracture risk in women. Osteoporos Int 15:942–947
31. **Prabhala A, Garg R, Dandona P** 2000 Severe myopathy associated with vitamin D deficiency in western New York. Arch Intern Med 160:1199–1203
32. **Rimaniol JM, Authier FJ, Chariot P** 1994 Muscle weakness in intensive care patients: initial manifestation of vitamin D deficiency. Intensive Care Med 20:591–592
33. **Delmont E, Roth S, Heudier P, Cua E, Kaphan R, Campagni JP, Lienhard-Labaune C, Heerding D, Fuzibet JG** 2001 [Primary hyperparathyroidism, a differential diagnosis of motor neuron diseases.] Rev Med Interne 22:1253–1255
34. **Center JR, Nguyen TV, Sambrook PN, Eisman JA** 2000 Hormonal and biochemical parameters and osteoporotic fractures in elderly men. J Bone Miner Res 15:1405–1411
35. **Hurley MV, Rees J, Newham DJ** 1998 Quadriceps function, proprioceptive acuity and functional performance in healthy young, middle-aged and elderly subjects. Age Ageing 27:55–62
36. **Hassan BS, Mockett S, Doherty M** 2001 Static postural sway, proprioception, and maximal voluntary quadriceps contraction in patients with knee osteoarthritis and normal control subjects. Ann Rheum Dis 60:612–618
37. **Lord SR, Sambrook PN, Gilbert C, Kelly PJ, Nguyen T, Webster IW, Eisman JA** 1994 Postural stability, falls and fractures in the elderly: results from the Dubbo Osteoporosis Epidemiology Study. Med J Aust 160:684–685, 688–691
38. **Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, Eisman J, Fujiwara S, Garnero P, Kroger H, McCloskey EV, Mellstrom D, Melton LJ, Pols H, Reeve J, Silman A, Tenenhouse A** 2004 A meta-analysis of previous fracture and subsequent fracture risk. Bone 35:375–382
39. **Klotzbuecher CM, Ross PD, Landsman PB, Abbott TAr, Berger M** 2000 Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res 15:721–739
40. **Robbins JA, Schott AM, Garnero P, Delmas PD, Hans D, Meunier PJ** 2005 Risk factors for hip fracture in women with high BMD: EPIDOS study. Osteoporos Int 16:149–154
41. **Cooper C** 1997 The crippling consequences of fractures and their impact on quality of life. Am J Med 103:12S–17S; discussion 17S–19S
42. **Nguyen TV, Center JR, Pocock NA, Eisman JA** 2004 Limited utility of clinical indices for the prediction of symptomatic fracture risk in postmenopausal women. Osteoporos Int 15:49–55
43. **Cummings SR, Melton LJ** 2002 Epidemiology and outcomes of osteoporotic fractures. Lancet 359:1761–1767
44. **Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA** 1999 Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 353:878–882

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.