

Mortality Risk Associated With Low-Trauma Osteoporotic Fracture and Subsequent Fracture in Men and Women

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OSTEOPOROTIC FRACTURES represent a growing public health problem in both developed and developing countries, with a projected increasing incidence as the population ages.^{1,2} The burden of fractures relates to the costs as well as the morbidity and associated mortality.^{1,3-5} The premature mortality following hip and vertebral fractures is now well recognized.^{5,6} However, premature mortality following other fracture types⁵⁻⁸ is less well appreciated.

Long-term (>5-year) mortality data following fractures are limited. For hip fracture, mortality is highest in the first year,⁸ and although controversial, may remain elevated for more than 10 years.⁹ Mortality following clinical vertebral fractures has been reported to be increased for up to 10 years in women and 3 years in men in a case-control study.¹⁰

Osteoporotic fracture also increases the risk of subsequent fracture,¹¹ but the effect of these subsequent fractures on mortality risk has not been systematically studied.

It remains unclear what drives the fracture-mortality association. Some studies suggest that a large part of the

Context There are few data on long-term mortality following osteoporotic fracture and fewer following subsequent fracture.

Objectives To examine long-term mortality risk in women and men following all osteoporotic fractures and to assess the association of subsequent fracture with that risk.

Design, Setting, and Participants Prospective cohort from the Dubbo Osteoporosis Epidemiology Study of community-dwelling women and men aged 60 years and older from Dubbo, Australia, who sustained a fracture between April 1989 and May 2007.

Main Outcome Measures Age- and sex-specific standardized mortality ratios (SMRs) compared with the overall Dubbo population for hip, vertebral, major, and minor fractures.

Results In women, there were 952 low-trauma fractures followed by 461 deaths, and in men, 343 fractures were followed by 197 deaths. Age-adjusted SMRs were increased following hip fractures (SMRs, 2.43 [95% confidence interval [CI], 2.02-2.93] and 3.51 [95% CI, 2.65-4.66]), vertebral fractures (SMRs, 1.82 [95% CI, 1.52-2.17] and 2.12 [95% CI, 1.66-2.72]), major fractures (SMRs, 1.65 [95% CI, 1.31-2.08] and 1.70 [95% CI, 1.23-2.36]), and minor fractures (SMRs, 1.42 [95% CI, 1.19-1.70] and 1.33 [95% CI, 0.99-1.80]) for both women and men, respectively. Mortality was increased for all ages for all fractures except minor fractures for which increased mortality was only apparent for those older than 75 years. Increased mortality risk persisted for 5 years for all fractures and up to 10 years for hip fractures. Increases in absolute mortality that were above expected, for 5 years after fracture, ranged from 1.3 to 13.2 per 100 person-years in women and from 2.7 to 22.3 per 100 person-years in men, depending on fracture type. Subsequent fracture was associated with an increased mortality hazard ratio of 1.91 (95% CI, 1.54-2.37) in women and 2.99 (95% CI, 2.11-4.24) in men. Mortality risk following a subsequent fracture then declined but beyond 5 years still remained higher than in the general population (SMR, 1.41 [95% CI, 1.01-1.97] and SMR, 1.78 [95% CI, 0.96-3.31] for women and men, respectively). Predictors of mortality after any fragility fracture for both men and women included age, quadriceps weakness, and subsequent fracture but not comorbidities. Low bone mineral density, having smoked, and sway were also predictors for women and less physical activity for men.

Conclusions In a sample of older women and men, all low-trauma fractures were associated with increased mortality risk for 5 to 10 years. Subsequent fracture was associated with increased mortality risk for an additional 5 years.

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fracture-mortality association is related to underlying health or comorbidities^{7,12} whereas others have found little or no evidence that underlying health plays a major part.^{6,9}

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Therefore, the aims of this study were to examine (1) the long-term mortality risk (up to 18 years) following all types of osteoporotic fractures in women and men in different age groups, (2) the association of subsequent fracture with that mortality risk, (3) what clinical factors present at the time of fracture predict mortality, and (4) the effect of fracture over and above low bone mineral density (BMD) on mortality.

METHODS

Study Population

The Dubbo Osteoporosis Epidemiology Study, started in 1989, is a longitudinal population-based study of women and men aged 60 years and older living in Dubbo, 400 km northwest of Sydney, Australia. The study was approved by the St Vincent's Hospital human research ethics committee. In 1989, the population was 32 000 and 98.6% white and had the same age and sex distribution as the Australian population. Dubbo's relative isolation, centralized health services, and stable population make it optimal for epidemiological research, and it is estimated that less than 6% of the population could have been lost to follow-up. A detailed description of the study design, general goals, and methodology has been previously published.^{13,14} Because of the nature of the study, none of the participants were living in institutions. The entire Dubbo population 60 years and older consisted of 2245 women and 1760 men in 1989 (FIGURE 1). Between April 1989 and May 2007, 952 women and 343 men sustained at least 1 minimal-trauma fracture.

Detailed Study Group

Of those who sustained a fracture, 452 women (47%) and 162 men (47%) agreed to participate in a detailed ongoing assessment after providing written informed consent and had data available close to the fracture event (Figure 1). Lifestyle factors, including physical activity, dietary calcium intake, cigarette smoking, and alcohol consumption; number of falls in the last

year; comorbid illnesses; and medications were assessed by questionnaire. Anthropometric measurements, bone mineral density (BMD), quadriceps strength, and sway were measured. Interview and measurements were carried out approximately every second year by a nurse coordinator at the study center. For this analysis, the variables (except for calcium intake and physical activity in which only baseline data were available) were those taken at a visit within 5 years prior to and 1 year following the fracture. Comorbidities were only analyzed if present at time of fracture. The median time between visit and fracture event was 9.7 months (interquartile range [IQR], 21.6 mo prior to and 1.6 mo after fracture) for women and 7.5 months (IQR, 19.2 mo prior to and 1.5 mo after fracture) for men. The median follow-up after the fracture was 13.1 years (IQR, 8.0-16.2) for women and 9.5 years (IQR, 5.3-15.0) for men.

Fracture Assessment and Mortality Data

Fractures were identified from x-ray reports obtained from the 2, and for some time 3, radiological services for the entire Dubbo area. Circumstances surrounding the fracture were obtained by personal interview. High-trauma fractures; potentially pathological fractures (eg, cancer or Paget disease); or fractures of the head, fingers, and toes were not analyzed.

Vertebral fractures were identified from x-ray but systematic screening was not performed. Vertebral fracture was considered clinical if there was a specific cause for the x-ray (eg, back pain) and incidental if this cause was not present. Approximately half of all vertebral fractures were clinical; 151 of 283 for women and 51 of 107 for men. Incident and prevalent vertebral fractures had similarly increased premature mortality in either proportional hazards or logistic regression models and hence were analyzed together.

Because several types of fractures are associated with increased mortality risk,⁵ fractures were analyzed in 4 sepa-

rate groups, ie, hip, vertebral, major, and minor fractures. Major fractures included pelvis, distal femur, proximal tibia, 3 or more simultaneous ribs, and proximal humerus. Minor fractures included all remaining osteoporotic fractures. Major and minor fractures were grouped together for some analyses as nonhip, nonvertebral fractures. If an individual had more than 1 fracture during 1 event, only the more "serious" fracture was considered. Major fractures for women included 15 multiple rib, 87 humeral, 22 pelvic, and 30 limb. For men, there were 24 multiple rib, 24 humeral, 8 pelvic, and 13 limb. Minor fractures for women included 165 forearm, 36 carpal/metacarpal, 37 rib, 62 distal lower limb, 23 foot, and 9 clavicle. For men there were 20 forearm, 9 carpal/metacarpal, 39 rib, 25 distal lower limb, 3 foot, and 8 clavicle.

Mortality status of all fracture participants was identified from systematic searches of funeral director lists, local newspapers, and Dubbo media reports and verified by death certificates from the New South Wales Registry of Births, Deaths and Marriages. Population at risk and mortality data for the whole Dubbo area were from the Australian Bureau of Statistics for each year of the study.

Statistical Analyses

Sex-specific mortality rates were calculated for the whole Dubbo population aged 60 years and older in 5-year age groups for each year of follow-up based on the actual number of deaths and midyear population obtained from the Australian Bureau of Statistics. Changes over time were evaluated in 0 to 5 years, 5 to 10 years, and 10 or more years of follow-up.

Age- and sex-specific mortality rates for each fracture group, based on the time from fracture event to death or end of the study, were compared with expected mortality from age- and sex-specific Dubbo population mortality rates (standardized mortality ratios [SMRs]). Significance and 95% confidence intervals (CIs) were calculated assuming a Poisson distribution. The

sample size had power of 90% or greater to detect a 2-fold relative risk increase.¹⁵

Kaplan-Meier survival curves, based on Dubbo population life tables, were constructed separately for women and men and stratified by fracture type, and differences were tested by log-rank statistic. Fracture participants were removed from the general population data to compare fracture participants with a nonfracture population.

Excess deaths for the fracture population were based on the difference between observed and expected number of deaths. Life years lost was estimated from the expected survival at age of fracture from Australian life tables.

Following a subsequent osteoporotic fracture, risk of mortality was evaluated in two 5-year follow-up intervals between subsequent fracture and death or end of the study. Subsequent fracture was also analyzed as a time-dependent variable in a Cox proportional hazards model for mortality.

Comorbidities and risk factors for mortality were analyzed in Cox proportional hazards models in the detailed study group. Forward and backward stepwise models and the Akaike information criterion were used to determine the most parsimonious models. The effect of fracture in addition to low BMD was assessed in an age-matched (± 1 year) and BMD-matched (± 0.02 g/cm²) subgroup of fracture and nonfracture participants using conditional logistic regression. All statistical analyses were performed using SAS version 9,¹⁶ and significance levels ($P < .05$) were 2-sided.

RESULTS

Fracture Incidence and Mortality Rates

There were 952 fractures in women and 343 in men for the Dubbo population aged 60 years and older over 29 660 and 20 717 person-years of observation, respectively (April 1989 through May 2007) (Figure 1). These equated to an average fracture incidence of 32 per 1000 person-years (95% CI, 30-34) in women and 17 per 1000 person-years (95% CI, 15-18) in men.

In the entire Dubbo population 60 years and older, 1609 deaths were recorded in women and 1514 in men over 37 406 and 27 409 person-years, yielding mortality rates of 4.3 per 100 person-years (95% CI, 4.1-4.5) and 5.5 per 100 person-years (95% CI, 5.3-5.8) in women and men, respectively. Among the fracture participants, 461 deaths were observed in women and 197 in men, yielding substantially higher mortality rates of 7.8 per 100 person-years (95% CI, 7.1-8.5) and 11.3 per 100 person-years (95% CI, 9.8-13.0) in women and men, respectively. For both sexes, these rates were highest following hip, vertebral, major, and then minor fractures, in that order (TABLE 1).

Mortality rates in both sexes increased with age as expected. However, for each age group, mortality in the fracture participants was consistently higher than that in the general population (FIGURE 2). For all ages, mortality was higher for men than for women, most markedly in the older age groups.

Absolute mortality rates were highest in the first 5 years following fracture, 8.9 per 100 person-years for women (95% CI, 7.9-9.9) and 14.5 per 100 person-years for men (95% CI, 12.4-17.0). These rates declined thereafter toward the expected mortality rates such that, of all observed deaths, 66%

in women and 78% in men occurred during these first 5 years. Increases in absolute mortality that were above expected in women over these 5 years after fracture ranged from 1.3 per 100 person-years for minor fractures to 13.2 per 100 person-years for hip fractures. In men, absolute mortality increases for the same period ranged from 2.7 to 22.3 per 100 person-years depending on fracture type.

For all fracture types, SMRs were elevated for the first 5 years, ranging from 1.38 to 2.53 in women and 1.64 to 3.52 in men with the highest SMR after hip

Figure 1. Dubbo Osteoporosis Epidemiology Study Population, 1989 Through 2007

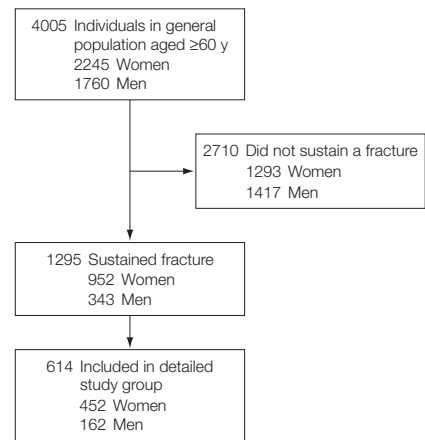


Table 1. Age-Adjusted Mortality Rate and Standardized Mortality Ratios According to Fracture Type

	Fracture Participants, No.	Deaths, No.	Person-Years	Mortality Rate per 100 Person-Years (95% CI)	SMR (95% CI)
Women					
General population		1609	37 406	4.30 (4.10-4.52)	
All fractures	952	461	5928	7.78 (7.10-8.52)	1.76 (1.59-1.95)
Hip	183	118	765	15.42 (12.88-18.52)	2.43 (2.02-2.93)
Vertebral	283	133	1483	8.97 (7.57-10.63)	1.82 (1.52-2.17)
Major ^a	154	77	990	7.78 (6.22-9.73)	1.65 (1.31-2.08)
Minor ^a	332	133	2690	4.95 (4.17-5.86)	1.42 (1.19-1.70)
Men					
General population		1514	27 409	5.52 (5.25-5.81)	
All fractures	343	197	1744	11.30 (9.82-12.99)	1.96 (1.69-2.28)
Hip	63	50	195	25.67 (19.46-33.87)	3.51 (2.65-4.66)
Vertebral	107	65	429	15.16 (11.89-19.33)	2.12 (1.66-2.72)
Major ^a	69	37	366	10.12 (7.33-13.97)	1.70 (1.23-2.36)
Minor ^a	104	45	755	5.96 (4.45-7.98)	1.33 (0.99-1.80)

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.
^aMajor fractures included pelvis, distal femur, proximal tibia, 3 or more simultaneous ribs, and proximal humerus. Minor fractures included all remaining osteoporotic fractures.

fracture, followed by vertebral, major, and minor fractures (TABLE 2). Mortality rates returned toward population mortality rates for the 5- to 10-year and greater-than 10-year intervals after the initial fracture for all fracture types but remained elevated after hip fractures for the 5- to 10-year interval postfracture: SMR, 1.52 (95% CI, 1.01-2.29) for women and 2.58 (95% CI, 1.29-5.17) for men. After 10 years, even after hip fracture, mortality rates were not different from that of an appropriately age-matched population (SMR, 0.89 [95% CI, 0.40-1.98] for women

and 0.78 [95% CI, 0.11-5.51] for men). Mortality rates for nonhip fractures returned to population mortality over the second 5 years with SMRs ranging from 0.8 for minor fractures to 1.3 for vertebral fractures. These changes are apparent in the Kaplan-Meier survival curves (FIGURE 3).

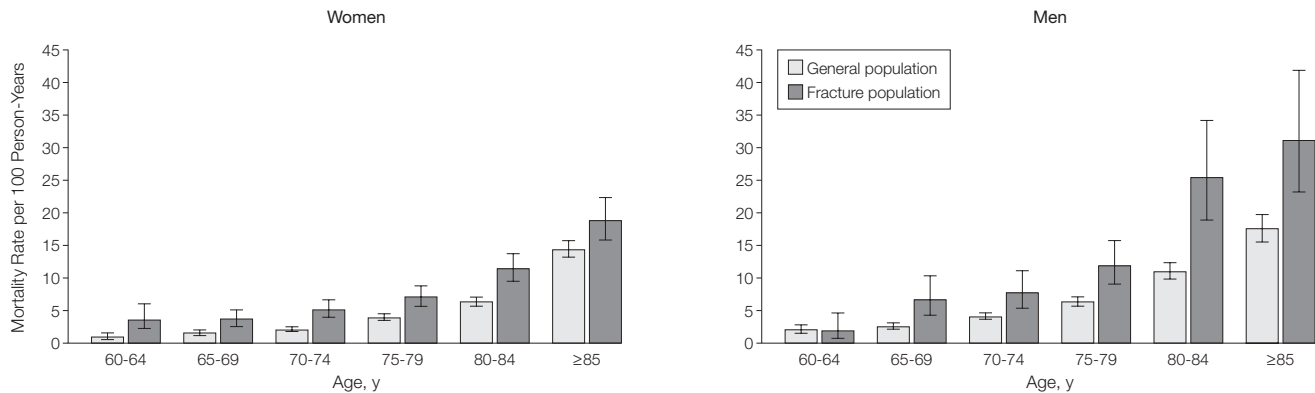
Premature mortality was observed across all age groups following hip, vertebral, and major fractures for 5 years postfracture except for minor fractures, where it was only apparent in the elderly (aged ≥ 75 years) (Table 2, Figure 3). In age groups older than 75

years, although hip fracture participants fared the worst ($P < .001$ for both women and men), survival was decreased to a similar extent for other fracture groups ($P = .49$ for women and $P = .73$ for men).

Nonhip, Nonvertebral Fractures

Of the 1295 total fractures, 659 were nonhip, nonvertebral fractures (74% in women and 26% in men). These fractures preceded 46% of all deaths in women and 42% in men. The overall SMRs were 1.50 (95% CI, 1.30-1.73) in women and 1.48 (95% CI, 1.18-1.85)

Figure 2. Mortality Rates for the General Population and Fracture Participants According to Age



In Dubbo's general population, there were 2245 women and 1760 men aged 60 years and older. Of the fracture participants, 952 were women and 343 were men. Error bars indicate 95% confidence intervals.

Table 2. Age-Adjusted Standardized Mortality According to Fracture Type for the First 5 Years After Fracture

Fracture Type	Women			Men		
	Deaths, No.	Person-Years	SMR (95% CI)	Deaths, No.	Person-Years	SMR (95% CI)
Hip						
All ages	89	509	2.53 (2.04-3.13)	41	147	3.52 (2.58-4.80)
60-74 y	12	84	8.28 (4.65-14.73)	5	55	2.43 (1.01-5.86)
≥ 75 y	77	425	2.24 (1.78-2.82)	36	92	3.65 (2.62-5.09)
Vertebral						
All ages	93	994	1.76 (1.43-2.17)	52	307	2.26 (1.72-2.98)
60-74 y	22	327	3.77 (2.45-5.81)	13	91	4.19 (2.42-7.27)
≥ 75 y	71	667	1.45 (1.14-1.84)	39	216	1.88 (1.37-2.59)
Major ^a						
All ages	48	591	1.60 (1.20-2.13)	28	209	2.01 (1.38-2.92)
60-74 y	13	227	3.23 (1.85-5.62)	7	105	2.22 (1.05-4.67)
≥ 75 y	35	364	1.31 (0.94-1.83)	21	104	1.80 (1.17-2.77)
Minor ^a						
All ages	76	1349	1.38 (1.10-1.74)	33	400	1.64 (1.16-2.31)
60-74 y	17	732	1.43 (0.88-2.33)	6	225	0.94 (0.42-2.11)
≥ 75 y	59	617	1.37 (1.06-1.78)	27	175	1.82 (1.24-2.66)

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.

^aMajor fractures included pelvis, distal femur, proximal tibia, 3 or more simultaneous ribs, and proximal humerus. Minor fractures included all remaining osteoporotic fractures.

in men, suggesting that nonhip, nonvertebral fractures contributed to 28% and 31% of all excess deaths in women and men, respectively. Mortality rates for 5 years after these fractures were higher than the general population for the older age groups (>75 years) in both women and men and for the younger age group (60-74 years) in women. Mortality following a nonhip, nonvertebral fracture was increased al-

most 2-fold (SMR, 1.81 [95% CI, 1.35-2.42]) in men older than 75 years with a similar, albeit nonsignificant, increase (SMR, 1.36 [95% CI, 0.79-2.37]) in younger men. Sensitivity analyses by exclusion of specific fracture types, such as metacarpal, metatarsal, or ankle fractures in women, did not materially alter the findings (data not shown).

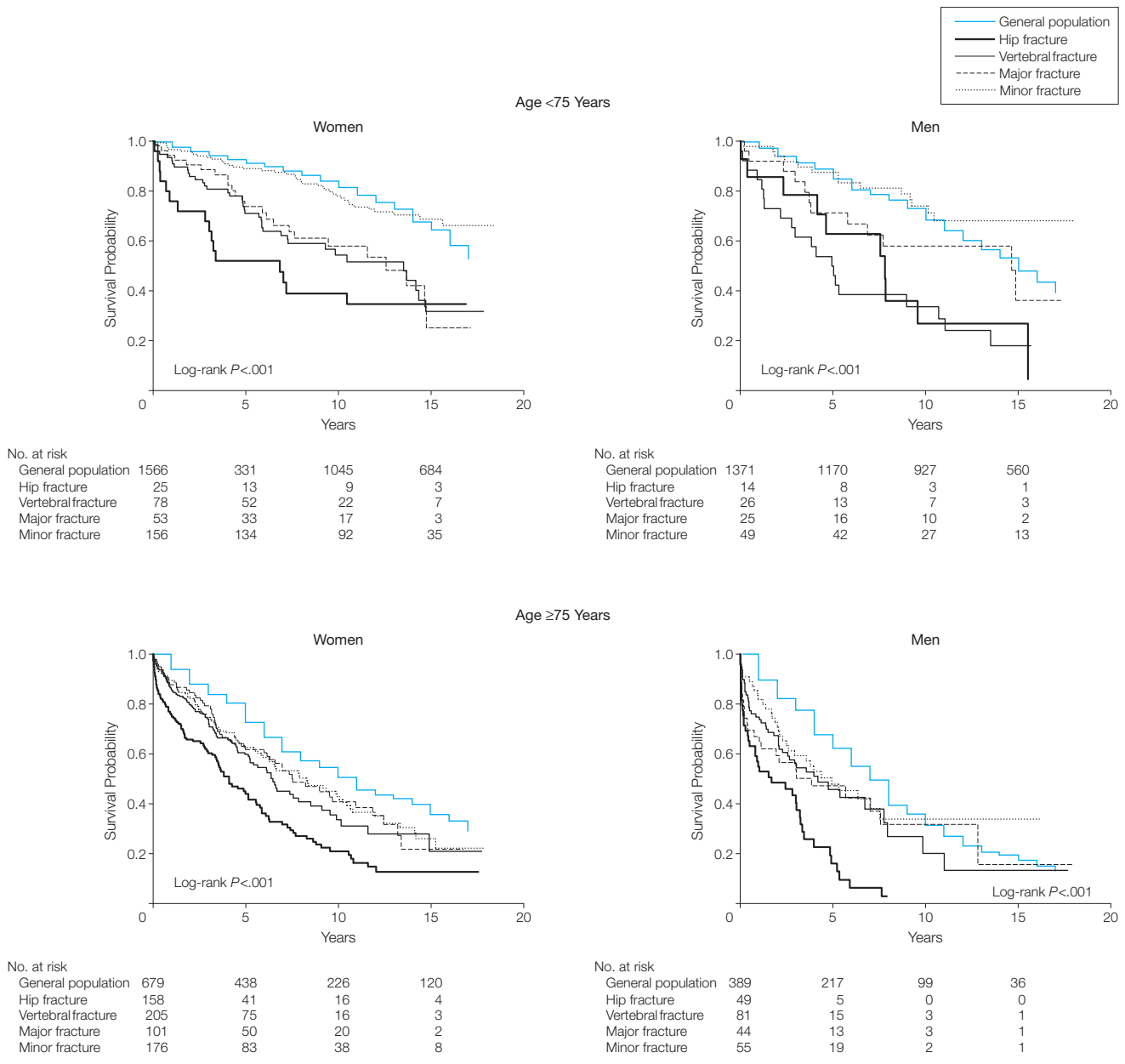
Rib fractures (52 in women and 63 in men) constituted a major grouping

within nonhip, nonvertebral fractures, with increased mortality in women (SMR, 2.26 [95% CI, 1.58-3.23]) and with a borderline increase in men (SMR, 1.37 [95% CI, 0.96-1.96]).

Subsequent Fractures and Mortality Risk

Approximately 30% of women (290/952) and 22% of men (74/343) experienced another fracture during the

Figure 3. Kaplan-Meier Survival Curves for the General and Fracture Populations According to Type of Fracture and Age Group



study period over a median of 5.1 years (IQR, 2.2-9.7). Of these, 143 women (49%) and 55 men (74%) died, yielding death rates of 11 per 100 person-years (95% CI, 9-13) for women and 18 per 100 person-years (95% CI, 14-24) for men.

Subsequent fracture was associated with an increased mortality hazard ratio (HR) of 1.91 (95% CI, 1.54-2.37) in women and 2.99 (95% CI, 2.11-4.24) in men. The 5-year mortality for those with a subsequent fracture (SMR, 2.21 [95% CI, 1.82-2.69] in women and 3.53 [95% CI, 2.62-4.74] in men) was greater than for those with only 1 fracture (SMR, 1.41 [95% CI, 1.23-1.61] for women and 1.82 [95% CI, 1.51-2.18] for men). Mortality risk following a subsequent fracture declined but beyond 5 years still remained higher than the

general population (SMR, 1.41 [95% CI, 1.01-1.97] and SMR, 1.78 [95% CI, 0.96-3.31] for women and men, respectively).

The majority of excess deaths related to fracture over the 18 years of observation occurred in the first 5 years (87%). Of the excess mortality in this first 5 years, hip, vertebral, and nonhip, non-vertebral fractures were each associated with approximately one-third of deaths (37%, 35%, and 29%, respectively).

The major causes of death from death certificates were 27% cardiac (n=204), 26% respiratory (n=193), 15% cerebrovascular (n=110), and 13% malignancy (n=98). Fracture was mentioned in only 10.5% of death certificates, primarily hip and vertebral fracture, and osteoporosis without a fracture in an additional 2.5%.

Detailed Study Group

The detailed study group comprised 47% of women and men with fracture (TABLE 3). The women in the detailed study group were somewhat younger (mean [SD] age, 77 [7] years vs 80 [8] years; P<.001) and had slightly lower SMRs (1.51 [95% CI, 1.30-1.74] vs 1.90 [95% CI, 1.63-2.21]). The men in the detailed study group were of similar age and had similar SMRs to that of the total fracture group. The distribution of fracture types was similar in these 2 groups.

Among the women and men with fractures, those who died were older, weighed less, and had lower bone density and weaker quadriceps. Women who died also had higher sway. Among those who died, there was more cardiovascular illness in women and more neurological and respiratory illness in men; however, neither type nor number of comorbidities (median equivalent in all groups) was predictive of postfracture mortality (Table 3).

Most, but not all, of the factors associated with increased mortality in univariate analyses (TABLE 4) also contributed in the multivariate analysis. The most parsimonious multivariate model, for both women and men, included advancing age (HRs, 1.36 [95% CI, 1.22-1.51] and 1.42 [95% CI, 1.20-1.68]), subsequent fracture (HRs, 1.53 [95% CI, 1.15-2.04] and 1.80 [95% CI, 1.12-2.89]) and weaker quadriceps (HRs, 1.20 [95% CI, 1.00-1.43] and 1.21 [95% CI, 1.01-1.46]) in women and men, respectively. For women, lower BMD (HR, 1.46 [95% CI, 1.24-1.72]), having smoked (HR, 1.35 [95% CI, 1.00-1.83]), and higher sway (HR, 1.14 [95% CI, 1.00-1.30]) and, for men, decreased physical activity (HR, 1.29 [95% CI, 0.97-1.70]) were also independent predictors of mortality (TABLE 5). In men, falling less was another independent predictor, presumably reflecting limited activity in a sicker subset.

Population attributable risk for mortality was greatest for low BMD in women (18% for T-score ≤-2.5). Subsequent fracture contributed 13% and 14% to the population attributable risk in women and men, respectively. Ever having

Table 3. Characteristics of Participants With Fracture in the Detailed Study Group

Variable	Women (n = 452)		Men (n = 162)	
	Dead (n = 202)	Alive (n = 250)	Dead (n = 97)	Alive (n = 65)
Age, mean (SD), y	79 (8) ^a	75 (7)	79 (7) ^b	76 (7)
Body mass index, mean (SD) ^c	25 (4) ^a	26 (5)	25 (4)	26 (4)
Femoral neck BMD, mean (SD), g/cm ² . ^d	0.67 (0.13) ^a	0.74 (0.10)	0.81 (0.13) ^a	0.89 (0.18)
Quadriceps strength, mean (SD), kg	16 (7) ^a	20 (8)	27 (10) ^a	34 (10)
Sway, median (IQR), cm ² . ^d	9.1 (5.3-33.6) ^b	7.9 (4.3-16.0)	7.4 (5.2-12.7)	9.0 (5.3-14.0)
Calcium intake, mean (SD), mg/d ^d	649 (382)	656 (365)	567 (370)	651 (397)
Physical activity, mean (SD), METs/d ^d	29 (3) ^a	31 (3)	31 (5) ^b	34 (5)
Fall, No. (%)	110 (54)	127 (51)	46 (47)	35 (54)
Smoker, ever, No. (%)	67 (33)	80 (32)	68 (70)	42 (65)
Diseases, No. (%)				
None	94 (47)	117 (47)	37 (38)	24 (37)
1	73 (36)	81 (32)	39 (40)	28 (43)
2	27 (13)	43 (17)	18 (19)	12 (18)
≥3	8 (4)	9 (4)	3 (3)	1 (2)
Cardiovascular	66 (33) ^e	59 (24)	26 (27)	25 (38)
Hypertension	94 (47)	139 (56)	29 (30)	24 (37)
Diabetes	19 (9)	23 (9)	8 (8)	3 (5)
Respiratory	20 (10)	34 (14)	17 (18)	6 (9)
Neurological	31 (15)	42 (17)	21 (22)	11 (17)
Cancer	16 (8)	37 (15)	13 (13)	10 (15)

Abbreviations: BMD, bone mineral density; IQR, interquartile range; METs, metabolic equivalents.

^aP<.001 for comparison between dead and alive.

^bP≤.01 for comparison between dead and alive.

^cCalculated as weight in kilograms divided by height in meters squared.

^dBone mineral density data were missing for 4 men, sway data were missing for 2 men, calcium intake was missing for 24 women and 10 men, and physical activity data were missing for 4 women.

^eP<.05 for comparison between dead and alive.

smoked accounted for 10% in women, and being in the worst quartile in any 1 of the other factors accounted for 7% or less of population attributable risk.

Age- and BMD-Matched Analysis

A subanalysis to explore the association between fracture and mortality over and above low BMD was performed for 347 female fracture and 129 male fracture participants with the same numbers of age- and BMD-matched controls. Those fracture participants who were unable to be matched (83 women and 29 men) were older and had lower BMD. Follow-up time was similar in women (median, 6.9 years for both groups) but slightly shorter in men with fractures than those without (median, 4.4 years vs 6.4 years; *P* = .02).

In women with fracture, the mortality rates in the 2 matched groups were higher than that of the general population but were similar between those with and without fractures (SMR, 1.44 [95% CI, 1.21-1.71] and 1.47 [95% CI, 1.23-1.75]; odds ratio, 1.12 [95% CI, 0.81-1.56]). In men, fracture participants had higher associated mortality rates than their nonfractured counterparts, which were similar to an age-matched population (SMR, 2.04 [95% CI, 1.63-2.56] and 1.13 [95% CI, 0.87-1.47]; odds ratio, 1.95 [95% CI, 1.15-3.30]).

COMMENT

This study reports mortality risk over an 18-year period following all types of osteoporotic fractures, including the impact of subsequent fracture, in both women and men in different age groups. Mortality risk was increased in the fracture group compared with the general population similar to previous data.^{5,6,17} However, this study demonstrated increased mortality associated with all major fractures at all ages and even with minor fractures in older age groups. Mortality was increased for the first 5 years following fractures before returning to population mortality rates for all fracture groups, except for hip fractures where mortality rates remained elevated for up to 10 years. Most importantly, a subsequent fracture again

resulted in an elevated mortality risk for a further 5 years.

The importance of these findings stem from the systematic study of long-term mortality patterns following all fracture types. Increased mortality following hip and vertebral fractures is consistent with initial 5-year data from the same cohort and other studies.^{5,6,8,18-24} Premature mortality following hip fractures has been reported particularly in the first year⁸ and for up to 10 years by others^{9,25-27} in some case-control studies. In the current study, 30% of all post-hip fracture deaths occurred in the first 6 months and 21% in the next 18 months. In 2 long-term case-control studies of vertebral fractures, increased mortality was reported for up to 10 years but not compared with the general population.^{10,21}

The increased mortality observed here following other major and minor fractures is not well appreciated. Indeed this is the first finding of an increased mortality associated with minor fractures, albeit in older age groups (>75 years). In previous analyses,⁵⁻⁸ minor fractures were not associated with an increase in mortality, possibly because lesser or no effect in younger women obscured the association.

Given these findings, more attention should be given to nonhip, non-vertebral fractures that constituted approximately 50% of all low-trauma fractures and were associated with more than 40% of all deaths. They are also associated with increased subsequent fracture risk, again contributing to the morbidity and mortality burden of fragility fractures.

Table 4. Univariate Analysis of Risk Factors for Mortality

Variable	Unit Change	HR (95% CI)	
		Women	Men
Subsequent fracture		1.99 (1.47-2.67)	2.74 (1.69-4.44)
Age, y	+5	1.55 (1.41-1.71)	1.57 (1.33-1.84)
Femoral neck BMD, g/cm ²	-0.12	1.70 (1.46-1.96)	1.33 (1.14-1.56)
Quadriceps strength, kg	-10.4	1.58 (1.35-1.86)	1.47 (1.24-1.74)
Sway, cm ²	+7.70	1.39 (1.21-1.58)	1.06 (0.86-1.31)
Falls, none/≥1		1.04 (0.79-1.37)	0.75 (0.50-1.11)
Smoking, yes/no		1.07 (0.80-1.44)	1.22 (0.79-1.88)
Physical activity, METs/d	-5.5	2.02 (1.45-2.81)	1.41 (1.09-1.84)
Body mass index	-5.0	1.26 (1.07-1.49)	1.32 (1.00-1.74)
Calcium, mg/d	-365	1.01 (0.88-1.16)	1.15 (0.92-1.45)
Diseases			
1 vs none		1.04 (0.70-1.56)	0.86 (0.50-1.46)
≥2 vs none		1.02 (0.69-1.51)	0.98 (0.57-1.68)

Abbreviations: BMD, bone mineral density; CI, confidence interval; HR, hazard ratio; METs, metabolic equivalents.

Table 5. Multivariate Analysis of Risk Factors for Mortality

Variable	Unit Change	HR (95% CI) ^a	
		Women	Men
Subsequent fracture		1.53 (1.15-2.04)	1.80 (1.12-2.89)
Age, y	+5	1.36 (1.22-1.51)	1.42 (1.20-1.68)
Femoral neck BMD, g/cm ²	-0.12	1.46 (1.24-1.72)	
Quadriceps strength, kg	-10.4	1.20 (1.00-1.43)	1.21 (1.01-1.46)
Sway, cm ²	+7.70	1.14 (1.00-1.30)	
Falls, none/≥1			0.59 (0.38-0.90)
Smoking, yes/no		1.35 (1.00-1.83)	
Physical activity, METs/d	-5.5		1.29 (0.97-1.70)

Abbreviations: BMD, bone mineral density; CI, confidence interval; HR, hazard ratio; METs, metabolic equivalents.
^aBlank cells indicate variables were not significant in the multivariate analyses and therefore were not selected for the final model.

When considering mortality outcomes following fracture over a prolonged follow-up, the 2- to 4-fold risk of occurrence of another fracture needs to be considered.^{11,28} In this study, although mortality risk returned to population levels over 5 years postfracture, a subsequent fracture again increased mortality risk 3- to 4-fold for a further 5 years.

The mechanism of the increased fracture-associated mortality remains uncertain. Some studies have suggested part or all of the mortality excess following hip fracture is related to the underlying health of the patient, including dementia, comorbid conditions, "frailty," weakness, and low bone density.^{7,12,29-31} Low bone density, a major risk factor for fracture, is independently associated with mortality.^{32,33} However, other studies have reported little or no relationship between mortality and underlying health.^{6,9,20,25,34} In Medicare beneficiaries with hip fracture, direct fracture-related mortality was apparent for the first 6 months, and all remaining short- and longer-term increased mortality was attributed to poorer underlying health.¹² In another study, direct fracture-associated mortality contributed up to 24% of all mortality.²² However, the fact that the excess mortality observed in the present study is highest immediately following almost all fragility fracture events and then declines, only to rise again following a subsequent fracture, supports a direct association with the events surrounding the fracture for at least part of the excess mortality.

The detailed subset analyses contribute to this issue. Subsequent fracture was a significant mortality predictor, in addition to age, in both sexes. The factors differentiating those female fracture participants who died compared with those who did not were lower BMD, weaker quadriceps, increased sway, or ever having smoked. In male fracture participants, weaker quadriceps and decreased physical activity were the independent predictors of mortality. While low BMD in women accounted for a large proportion of the associated postfracture mortality with a population at-

tributable risk of 18%, the factors analyzed did not completely account for increased premature mortality. However, comorbidities present at the time of fracture did not contribute to associated postfracture mortality.

In the subgroup of fracture participants matched by age and BMD to a nonfracture group, fracture was not associated with increased premature mortality in addition to low BMD in women. Thus, in this group of women with low BMD, fracture is a signal of an underlying high mortality risk. By contrast in men, fracture—and not low BMD—predicted mortality. This suggests that in men, fracture per se accounts for a significant proportion of associated mortality.

This study was not specifically designed to examine the underlying causes of mortality; however, examination of death certificates suggested no difference between causes of death in the fracture group and the general population, with cardiac, respiratory, cerebrovascular, and malignancy being the major causes. It still remains to be determined exactly what is responsible for the increased mortality following fracture.

A recent randomized study of bisphosphonate treatment of men and women soon after a hip fracture reported significantly decreased mortality.³⁵ Subsequent fracture is clearly an important risk for associated premature mortality, and therefore its prevention may contribute to a decrease in overall excess mortality.

The overall importance of excess fracture-associated mortality relates to the population mortality burden. Fracture rates clearly increase with age, as does mortality. However, the population structure is skewed in absolute number terms toward the younger age group, and thus excess deaths in this younger age group, although not as high as in the elderly, contribute substantially to potential years of life lost.

This study has a number of major strengths. It was in a large, stable population followed prospectively for 18 years, which allowed mortality risk estimates to be compared across sexes and

different age groups for different fracture groupings. The collection and verification of fracture and mortality data meant that ascertainment of events was highly reliable. Additionally, it was only with the long follow-up period that the prospective examination of subsequent fracture on mortality risk was possible. The longer follow-up in the matched group of the male nonfracture subjects excluded a follow-up bias.

There are some limitations. The population was almost entirely white, so the findings might not be generalizable to other ethnic groups. The mortality rates of the fracture participants were compared with the mortality rates of an age-matched general population, which therefore included some individuals with fracture, potentially underestimating the excess associated mortality.

CONCLUSION

This study demonstrated increased mortality following all major types of fragility fractures and even after minor fractures with older age. Mortality risk was highest in the first 5 years following all types of fractures, decreasing toward background population mortality risk, with hip fracture-associated mortality remaining elevated for up to 10 years. Nonhip, nonvertebral fractures, generally not considered in these types of studies, not only constituted almost 50% of the fractures studied, but also were associated with 29% of the premature mortality. Mortality risk decreased with time; however, the occurrence of a subsequent fracture was associated with a 3- to 4-fold increased mortality risk for a further 5 years. These data suggest fracture is a signal event that heralds an increased mortality risk: whether it is related to an underlying increased risk for both fracture and mortality, which may be the case for women, or whether it is related to some aspect of the fracture event itself, as appears to be the case for men, needs further exploration. Overall, this study highlights the premature mortality associated with all types of fractures, particularly that which occurs after subsequent fracture across the whole age spectrum of older men and women.

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REFERENCES

1. The burden of brittle bones: costing osteoporosis in Australia. Prepared for Osteoporosis Australia by Access Economics Pty Ltd, Canberra, 2001. <http://www.arthritisaustralia.org.au/Resources/Osteoporosis%20Reports/Brittle%20Bones.pdf>. Accessed January 2, 2009.
2. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet*. 2002;359(9319):1761-1767.
3. Cooper C. The crippling consequences of fractures and their impact on quality of life. *Am J Med*. 1997;103(2A):125-175.
4. Randell AG, Nguyen TV, Bhalerao N, Silverman SL, Sambrook PN, Eisman JA. Deterioration in quality of life following hip fracture: a prospective study. *Osteoporos Int*. 2000;11(5):460-466.
5. Center JR, Nguyen TV, Schneider P, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet*. 1999;353(9156):878-882.
6. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D. Risk of mortality following clinical fractures. *Osteoporos Int*. 2000;11(7):556-561.
7. Browner WS, Pressman AR, Nevitt MC, Cummings SR. Mortality following fractures in older women: the study of osteoporotic fractures. *Arch Intern Med*. 1996;156(14):1521-1525.
8. Johnell O, Kanis JA, Oden A, et al. Mortality after osteoporotic fractures. *Osteoporos Int*. 2004;15(1):38-42.
9. Vestergaard P, Rejnmark L, Mosekilde L. Increased mortality in patients with a hip fracture: effect of pre-morbid conditions and post-fracture complications. *Osteoporos Int*. 2007;18(12):1583-1593.
10. Hasselius R, Karlsson MK, Jonsson B, Redlund-Johnell I, Johnell O. Long-term morbidity and mortality after a clinically diagnosed vertebral fracture in the elderly: a 12- and 22-year follow-up of 257 patients. *Calcif Tissue Int*. 2005;76(4):235-242.
11. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. *JAMA*. 2007;297(4):387-394.
12. Tosteson AN, Gottlieb DJ, Radley DC, Fisher ES, Melton LJ III. Excess mortality following hip fracture: the role of underlying health status. *Osteoporos Int*. 2007;18(11):1463-1472.
13. Simons LA, McCallum J, Simons J, et al. The Dubbo study: an Australian prospective community study of the health of elderly. *Aust N Z J Med*. 1990;20(6):783-789.
14. Jones G, Nguyen T, Sambrook PN, Kelly PJ, Gilbert C, Eisman JA. Symptomatic fracture incidence in elderly men and women: the Dubbo Osteoporosis Epidemiology Study (DOES). *Osteoporos Int*. 1994;4(5):277-282.
15. Woodward M. Formulae for sample size, power and minimum detectable relative risk in medical studies. *Statistician*. 1992;41:185-196.
16. *Base SAS: 9.1.3 Procedures Guide*. 2nd ed. Cary, NC: SAS Publishing; 2006.
17. Haentjens P, Johnell O, Kanis JA, et al. Network on Male Osteoporosis in Europe (NEMO). Evidence from data searches and life-table analyses for gender-related differences in absolute risk of hip fracture after Colles' or spine fracture: Colles' fracture as an early and sensitive marker of skeletal fragility in white men. *J Bone Miner Res*. 2004;19(12):1933-1944.
18. Pongchaiyakul C, Nguyen ND, Jones G, Center JR, Eisman JA, Nguyen TV. Asymptomatic vertebral deformity as a major risk factor for subsequent fractures and mortality: a long-term prospective study. *J Bone Miner Res*. 2005;20(8):1349-1355.
19. Forsen L, Sogaard AJ, Meyer HE, Edna T, Kopjar B. Survival after hip fracture: short- and long-term excess mortality according to age and gender. *Osteoporos Int*. 1999;10(1):73-78.
20. Epana JP, Dargent-Molina P, Breart G; EPIDOS Group. Effect of hip fracture on mortality in elderly women: the EPIDOS prospective study. *J Am Geriatr Soc*. 2004;52(5):685-690.
21. Kado DM, Browner WS, Palermo L, Nevitt MC, Genant HK, Cummings SR; Study of Osteoporotic Fractures Research Group. Vertebral fractures and mortality in older women: a prospective study. *Arch Intern Med*. 1999;159(11):1215-1220.
22. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK. The components of excess mortality after hip fracture. *Bone*. 2003;32(5):468-473.
23. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B. Excess mortality after hospitalisation for vertebral fracture. *Osteoporos Int*. 2004;15(2):108-112.
24. Trone DW, Kritiz-Silverstein D, von Muhlen DG, Wingard DL, Barrett-Connor E. Is radiographic vertebral fracture a risk factor for mortality? *Am J Epidemiol*. 2007;166(10):1191-1197.
25. Farahmand BY, Michaelsson K, Ahlbom A, Ljunghall S, Baron JA; Swedish Hip Fracture Study Group. Survival after hip fracture. *Osteoporos Int*. 2005;16(12):1583-1590.
26. Karagiannis A, Papakitsou E, Dretakis K, et al. Mortality rates of patients with a hip fracture in a southwestern district of Greece: ten-year follow-up with reference to the type of fracture. *Calcif Tissue Int*. 2006;78(2):72-77.
27. Trombetti A, Herrmann F, Hoffmeyer P, Schurch MA, Bonjour JP, Rizzoli R. Survival and potential years of life lost after hip fracture in men and age-matched women. *Osteoporos Int*. 2002;13(9):731-737.
28. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA III, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res*. 2000;15(4):721-739.
29. Kado DM, Duong T, Stone KL, et al. Incident vertebral fractures and mortality in older women: a prospective study. *Osteoporos Int*. 2003;14(7):589-594.
30. Ensrud KE, Ewing SK, Taylor BC, et al; for the Study of Osteoporotic Fractures Research Group. Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. *J Gerontol A Biol Sci Med Sci*. 2007;62(7):744-751.
31. Cawthon PM, Marshall LM, Michael Y, et al; Osteoporotic Fractures in Men Research Group. Frailty in older men: prevalence, progression, and relationship with mortality. *J Am Geriatr Soc*. 2007;55(8):1216-1223.
32. Browner WS, Seeley DG, Vogt TM, Cummings SR; Study of Osteoporotic Fractures Research Group. Non-trauma mortality in elderly women with low bone mineral density. *Lancet*. 1991;338(8763):355-358.
33. Nguyen ND, Center JR, Eisman JA, Nguyen TV. Bone loss, weight loss, and weight fluctuation predict mortality in elderly men and women. *J Bone Miner Res*. 2007;22(8):1147-1154.
34. Ensrud KE, Thompson DE, Cauley JA, et al; Fracture Intervention Trial Research Group. Prevalent vertebral deformities predict mortality and hospitalization in older women with low bone mass. *J Am Geriatr Soc*. 2000;48(3):241-249.
35. Lyles KW, Colon-Emeric CS, Magaziner JS, et al; HORIZON Recurrent Fracture Trial. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med*. 2007;357(18):1799-1809.