Two-thirds of all fractures are not attributable to osteoporosis and advancing age: implication for fracture prevention

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ABSTRACT

Context: Although bone mineral density (BMD) is **strongly associated** with fracture and post-fracture mortality, the burden of fractures attributable to low BMD has not been investigated.

Objectives: We sought to estimate the population attributable fraction (PAF) of fractures and fracture-related mortality that can be attributed to low BMD.

Design and setting: This study is a part of an ongoing population-based prospective cohort study, Dubbo Osteoporosis Epidemiology study. In total, 3700 participants aged from 50 years and older had participated in the study. Low-trauma fracture was ascertained by X-ray reports, and mortality was ascertain from the Birth, Death and Marriage Registry.

Results: Overall, 21% of women and 11% of men had osteoporotic BMD. In univariable analysis, 21% and 16% of total fractures in women and men, respectively, were attributable to osteoporosis. Osteoporosis combined with advancing age (>70 yrs) accounted for 34% and 35% of fractures in women and men, respectively. However, these two factors accounted for ~60% of hip fractures. About 99% and 66% of postfracture mortality in women and men, respectively, were attributable to advancing age, osteoporosis and fracture; however, most of the attributable proportion was accounted for advancing age.

Conclusions: A substantial health care burden of fracture is on individuals aged <70 years and/or non-osteoporosis, suggesting that treatment of individuals with osteoporosis is unlikely to reduce a large number of fractures in the general population.

Précis

We defined the contribution of low BMD to fractures and post-fracture mortality. While only ~35% of fractures were attributable to low BMD and advancing age, most of postfracture death was attributable to advancing age

INTRODUCTION

It has been known for decades that low bone mineral density (BMD) is the most robust and reproducible predictor of fracture risk [1]. Each standard deviation lower BMD is associated with an average 2-fold increase in fracture risk [2]. This magnitude of association is actually equivalent to the magnitude of association between blood pressure and stroke [3]. Therefore, measurement of BMD has been used to operationally diagnose osteoporosis [4]. According to the World Health Organization, an individual with BMD T-score is classified into one of the following three categories: "normal" is a T-score greater than -1; "osteopenia" is between -2.5 and -1.0; and "osteoporosis" is a T-score of -2.5 or lower [4]. Moreover, treating individuals with osteoporotic BMD reduces their risk of fracture [5]. Thus, it can be said that the relationship between low BMD and fracture is likely to be causal.

Nevertheless, it has become apparent that a majority of fractures occur in non-osteoporotic individuals [6-9], and this was also the case for hip fracture[7]. In our previous study, approximately 55% of women and ~70% of men who sustained a fracture had "normal" or "osteopenic" BMD [10]. The National Osteoporosis Risk Assessment (NORA) observed that more than two-thirds of hip fracture patients did not have osteoporotic BMD (i.e., they had osteopenia or normal BMD) [11]. In the Study of Osteoporotic Fractures, more than 55% of osteoporotic fractures occurred in women with normal or osteopenic BMD [12]. Taken together, these data consistently suggest that, in absolute terms, most fractures occur in those with BMD above the “osteoporotic” cut-point.

The observation that a majority of fractures occurs in non-osteoporotic individuals is actually a realization of the idea of "*sick individuals and sick population*" that was articulated by

Rose in 1985 [13] . In that influential essay, Rose postulates that when the relationship between a risk factor and disease is continuous, a truncation of the distribution of the risk factor into "low risk" vs "high risk" group will result in the majority of disease cases in the "low risk" rather than in the high risk group. Consequently, preventive strategies focusing on the high risk group will produce limited utility.

From a public health point of view, the important questions are: How many fractures are attributable to low BMD? Is the magnitude of association between BMD and fracture risk constant over time? Does the attributable risk change with time? These questions have not been formally addressed. However the answers to these questions are highly relevant to assessing the potential impact of low BMD in the general population. The attributable fraction is theoretically dependent on two parameters, namely, the strength of association and the prevalence of the predictive factor. The strength of association between fracture and BMD is, in turn, dependent on fracture site. For instance, the magnitude of association between proximal femoral BMD and hip fracture is greater than that of proximal femoral BMD and non-hip fracture [12]. The primary aim of this study is to estimate the time-related proportion of fractures attributable to low proximal femoral BMD in the elderly population.

STUDY DESIGN AND METHODS

Study design and setting

This study was part of the Dubbo Osteoporosis Epidemiology Study (DOES) in which the protocol and study design have been described elsewhere [14]. Briefly, in late 1989, all Dubbo

residents aged 60 years and older were invited to participate in the study. Dubbo, lying 400 km northwest of Sydney (Australia), at that time had a population of approximately 32,000 people, of whom 98.6% were of Caucasian background. This city was selected for the study because the age and sex distribution of population closely resembled the Australian population, and it is relatively isolated in terms of medical care so that every fracture in the population could be practically ascertained [15]. The study's procedure and protocol were approved by the St Vincent's Campus Research Ethics Committee, and written informed consent was obtained from each participant.

Ascertainment of fracture

The primary outcome of this study is fragility fracture, which is defined as a fracture resulting from a fall from a standing height or less. The incidence of fractures had been ascertained from 1990 through X-ray reports provided by the two, and at times, three, local radiology centers and medical records [16]. The radiology centers did not exclusively specialize in bone disease. Fractures were included only if the report of fracture was definite and, confirmed on interview that it had occurred with low trauma. We excluded fractures from analysis if that resulted from major trauma (e.g., motor vehicle accident) or those related to disease as cancer or bone-related diseases, or those of digit, skull, or cervical spine. In this study, we focused primarily on hip fracture, vertebral fracture and wrist fracture because of their common frequency to ensure adequate statistical power for analysis of association.

Measurement of bone mineral density

At baseline, bone mineral density (BMD – g/cm^2) measurement was performed in the lumbar spine or femoral neck by dual-energy X-ray absorptiometry (DXA) using a DPX densitometer (GE LUNAR Madison, WI, USA). Radiation dose was less than 0.1 μGy. In normal subjects, the coefficient of variation for bone mineral density at our institution is 1-5% and 1-3% for lumbar spine and femoral neck, respectively [16]. However, only baseline femoral neck BMD, not lumbar spine BMD, was used in this study in order to minimize artefact due to degenerative changes artificially elevating BMD [17,18]. Other risk factors, including age, history of fracture after 50 years old, and history of falls in the previous 12 months, were collected from a structured questionnaire provided by nurse coordinators. Anthropometric variables (i.e., height and weight) of participants were also recorded.

Data analysis

As mentioned earlier, the population attributable fraction (PAF) is defined by two primary parameters: the prevalence of low BMD and the strength of association between low BMD and fracture. We varied the threshold of "low BMD" by T-scores <-2.5, -2.0, and -1.5. The strength of association was estimated by the hazard ratio from the Cox's proportional hazards model, in which the time to fracture was modeled as an exponential function of low BMD status and covariates. The covariates considered in the analysis were age, prior fracture, and fall. From the two parameters, the PAF was estimated by the time-dependent method [19,20] as implemented in the R package AF [21]. The method introduced by Hanley [22] was also used to calculate PAF because this method is able to delineate multiple exposures at the same time. The formula of the approach is:

$PAF = \frac{P_i(RR_i - 1)}{1 + \sum_{i=1}^{k} P_i(RR_i - 1)}$, where P_i is the prevalence of a risk factor i (i=1, 2, ..., k) ; and RR_i is the risk ratio of fracture associated with the risk factor [22]. All statistical analyses were conducted with R Statistical Environment [23].

RESULTS

Baseline characteristics of participants

The study included 2,320 women and 1,380 men, all aged 50 years and above at the time of study entry. The average age of all participants was ~69 years (SD 7.4). Based on the criteria of T-scores ≤ −2.5, 21% of women and 11% of men were classified as having osteoporotic BMD at baseline. During the follow-up period, approximately 37% (n = 864) of women and 20% of men (n = 273) had sustained a fragility fracture. Most fractures were observed at the vertebrae (~48% of all fractures in both sexes), followed by hip (~22%) and wrist (9%) of all fractures in women and in men (**Table 1**). A detailed analysis of fracture incidence by baseline risk factors is shown in Appendix I.

Hazard of fracture

The magnitude of association between baseline femoral neck BMD and fracture risk stratified by time of follow-up is shown in **Table 2**. In women, each standard deviation lower FNBMD was associated with an 80% increase in the hazard of fracture (HR 1.81; 95% CI, 1.58 to 2.06) within 5 years. The association between baseline FNBMD and fracture remained statistically

significant in 15 years later. The magnitude of association between baseline BMD and fracture and its decline with time were also observed in men.

The magnitude of association between baseline BMD and hip fracture risk was greater compared with that for vertebral and wrist fractures. The average hazard ratio for hip fracture during the first 5 years after hip BMD measurement was 3.5 in women and 2.6 in men, which were **significantly** higher than those for vertebral fracture (hazard ratio averaged at 2.0 in women and 2.3 in men) or wrist fracture (hazard ratio averaged at 1.6 in women and 1.1 in men). In fact, partly related to smaller number of events in men, the association between baseline BMD and wrist fracture was not statistically significant **(Table 2)**

Fracture attributable to low BMD or "osteoporosis"

The attributable fraction for fracture to osteoporotic BMD decreased over time (**Figure 1**). In women, approximately 20% of fractures could be attributed to osteoporotic BMD within the 1st year. The proportion slightly decreased to 17% in the 5th year, 14% in the 10th year, 11% in the 15th year and 19% in the 20th year. In men, the proportion of total fractures attributable to osteoporosis was 13% during the first year, and this was decreased to 8% after 20 years.

Analysis by fracture type revealed that the attributable fraction of fracture was highest for hip fracture, followed by vertebral fracture, any fracture and wrist fracture. In the 1st year, in women, ~41% of hip fracture was attributed to low BMD, followed by 22%, 19% and 15% of vertebral and any fracture, respectively (Appendix II). In men, the proportion of hip fractures attributable to low BMD was 22%, and this was progressively decreased to 18% in the 20th year.

For non-hip fractures, the population attributable fraction was lower for vertebral fracture (22% in women and 14% in men) and wrist fracture (11% in men).

Fractures attributable to low BMD and advancing age

However, lower bone mineral density is associated with advancing age. Moreover, advancing age and low BMD are known to be the most robust risk factors for fragility fracture. Therefore, next we addressed the question of how many fractures were attributable to advancing age (defined as 70 years and older) and low BMD. Using the Hanley's method [22], we found that ~34% and ~35% of total fractures in women and men, respectively, were attributable to advancing age and/or low BMD (**Table 3**). However, a decomposition analysis reveals that the majority of this attributable fraction was ascribed to advancing age. For instance, out of the 34% attributable fraction in women, approximately 19% were ascribed to advancing age *and* low BMD, and another 9% to advancing age alone (i.e., in the absence of low BMD). A similar trend was also observed in men.

Analysis for hip fracture revealed a different pattern: 63% of all hip fractures in women and 56% of all hip fracture in men were attributable to advancing age and/or low BMD. Again, a majority of this fracture was ascribed to advancing age in the presence or absence of low BMD. For vertebral fracture, about one third of cases in women and men were attributable to advancing age and/or low BMD.

There were a substantial difference in the age-and/or-low BMD attributable fraction for wrist fracture between genders. In women, just above 12% of wrist fractures were attributable to either advancing age or low BMD; in men, this proportion was less than 1%. As in the case of hip

and vertebral fractures, advancing age contributed to most of the attributable fraction in women. However, the differences were not statistically significant.

Mortality attributable to fracture, low BMD and advancing age

As mentioned earlier, fracture is associated with increased risk of mortality, and we would like to delineate the proportion of mortality attributable to fracture, low BMD and advancing age. Overall, 99% and 66% of post-fracture deaths in women and men, respectively, were attributable to the combination of the three factors: advancing age, low BMD, and fracture itself. Most of this fraction (88% in women and 63% in men) were ascribed to advancing age in the absence or presence of low BMD and fracture (**Table 4**).

In the absence of advancing age and low BMD, fracture alone accounted for 5.5% and 0.6% of all post-fracture deaths in women and men, respectively. When fracture was combined with advancing age and low BMD, the three factors collectively accounted for 45% and 18% of all post-fracture deaths in women and men, respectively.

DISCUSSION

Although the strong association between low BMD or osteoporosis and fracture has long been recognized, the proportion of fractures attributable to osteoporosis has not been systematically investigated. In this long-term study, we demonstrated that only 16% of total fractures in women and 15% of total fractures in men were attributable to low BMD (defined as BMD T-score ≤ -2.5). When low BMD was combined with advancing age, the two factors

accounted for approximately one third of all fractures. In other words, advancing age and osteoporosis did not capture 65% of all fracture cases.

An immediate question arises as what other factors account for the majority of fracture cases. In our study, only ~50% of all fractures occurred in those with at least one risk factor (i.e., aged 70+ years and/or osteoporosis). Fall is obviously an important factor for hip fracture[24], and the incidence of fall can be as high as 30% per year[25]. A history of fall was associated with a 4-fold increase in fracture risk[26]. Thus, it can be estimated that up to 47% of hip fractures are attributable to fall. Apart from fall, other factors such as lack of physical activity, poor grip strength, a history of hyperthyroidism, and low body mass index were also risk factors for fracture in non-osteoprotic women, but the magnitude of association for these risk factors was modest[7]. Genetic factors are known to affect fracture risk, but all the common variants identified so far explained less than 10% of fracture liability[27]. Taken together, our knowledge of risk factors that account for all fragility fractures is still limited.

Although low BMD has been recognized as the most robust risk factor for fragility fracture, it has recently been shown that a majority of fractures actually occur in those without osteoporotic BMD. In this study we confirm that observation. Indeed, almost 73% of women and 94% of men who had sustained a fracture did not have osteoporotic BMD at baseline (Appendix I). Moreover, almost 53% of women and 90% of men who sustained a fracture had BMD T-scores higher than -2.0. These observations underline the fact that the relationship between BMD and fracture risk is a continuous one, and that there is not really a clear cut-off value that defines high risk versus low risk. **This finding also underscores the idea that fracture risk assessment for an individual should consider BMD as a continuous variable rather based on arbitrary classification.**

We also observe that the magnitude of association between BMD and fracture risk declined with time from the baseline BMD measurement. The relative risk of fracture declined by ~50% in women and 60% in men between the first and 15th year of follow-up. In fact, for vertebral fracture (in men) and wrist fracture the association between baseline BMD and fracture risk after 20 years was not statistically significant. Our results are consistent with the findings of Black et al [28] in which the average hazard ratio for hip fracture was 2.6 over the period of 0-5 years, and progressively decreased to 1.8 over the period of 20-25 years and Stone et al [29] in which the age-adjusted relative hazard decreased from ~2.5 within the follow-up time less than 5 years to ~2 after 5 years of follow-up. Taken together, these results indicate that BMD has a good predictive value of fracture when it is measured close to the event.

It has increasingly been recognized that fragility fracture is an important risk factor for mortality. Indeed, individuals with a fragility have a two- to three-fold increase in mortality [30,31]. In this study, we have demonstrated that the proportion of post-fracture deaths was mainly attributable to advancing age. Indeed, advancing age in the absence or presence of low BMD and advancing age explained almost 100% of all postfracture deaths in women and more than three third in men In the absence of advancing age and low BMD, fracture itself accounted for only 5% and ~0.5% of all postfracture deaths in women and men, respectively. Moreover, in the absence of advancing age and fracture, low BMD accounted for just approximately 1% of all post-fracture deaths in women and men. Taken together, our data point out that fracture is indeed a risk factor for postfracture mortality, but the majority of this attributable fracture is due to advancing age. Age can be considered an index of cumulative exposure to environmental factors and stress.

Advancing age is also associated with more comorbidities[32], some of which may affect the risk of mortality. However, in a recent analysis[33] we found that comorbidities (eg cardiovascular disease, diabetes, stroke, thrombosis and cancer) accounted for only 9.2% and 5% of total mortality in women and men, respectively.

The present findings should be interpreted within context of strengths and weaknesses. A strength of this study is that the results were derived from a well characterized cohort and a long term follow-up. Moreover, we could ascertain fracture by X-ray report to avoid misclassification. However, the number of wrist fractures is relatively small which could result in unstable estimate of attributable fraction. It could be argued that the dichotomization of age and bone mineral density is arbitrary (as there is no clear cut-off value to define 'advancing age'). However, the dichotomization is technically necessary for estimating the attributable risk fraction. We would also like to note that the study population was of Caucasian background aged 60 years and older, and the magnitude of association between risk factors and fracture may be ethnicity-dependent; thus the present findings may not be relevant to younger population or non-Caucasian populations.

In conclusion, these data suggest that a substantial health care burden of fragility fractures is on individuals under the age of 70 and/or non-osteoporotic BMD, suggesting that treatment of men and women with osteoporotic BMD is unlikely to reduce a large number of fractures in the general population. Population-based prevention targetting those at highest absolute risk is likely to be more effective in reducing health care burden of fracture than treating individuals with single risk factors (eg osteoporosis) alone.

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Table 1: Baseline characteristics of 2320 women and 1380 men

Variable	Women	Men
N	2320	1380
Age (mean, SD)	68.7 (7.7)	68.9 (6.7)
Body mass index (mean, SD)	26.4 (5.2)	26.9 (4.1)
Femoral neck BMD (mean, SD)	0.81 (0.14)	0.92 (0.1)
Prevalence of osteoporotic BMD (n, %)	483 (21.3)	143 (10.7)
Incidence of fractures (n, %)		
• Any fracture	864 (37.2)	273 (19.8)
• Hip fracture	188 (21.7)	62 (22.7)
• Vertebral fracture	416 (48.1)	129 (47.3)
• Wrist fracture	92 (10.6)	13 (4.8)

Notes: Osteoporosis was defined as femoral neck T-score ≤ -2.5; SD: standard deviation.

Table 2: Association between bone mineral density at baseline and fracture: Hazard ratio of fracture by time, stratified by sex

	0 - 5 year	5 - 10 year	10 - 15 year	15+ year
Any fracture				
Women	1.8 (1.6 , 2.1)	1.5 (1.3 , 1.8)	1.5 (1.2 , 1.8)	1.3 (1.1 , 1.7)
Men	1.8 (1.5 , 2.3)	1.3 (1.0 , 1.7)	1.4 (1.0 , 1.9)	1.2 (0.9 , 1.7)
Hip fracture				
Women	3.5 (2.4 , 5.2)	3.5 (2.4, 5.2)	2.0 (1.3 , 3.3)	1.3 (0.9 , 1.8)
Men	2.6 (1.5 , 4.5)	2.9 (1.7 , 5.0)	2.1 (1.2, 3.6)	1.8 (1.1 , 2.9)
Vertebral fracture				
Women	2.0 (1.6 , 2.6)	1.4 (1.1 , 1.7)	1.6 (1.3 , 2.0)	1.5 (1.1 , 2.0)
Men	2.3 (1.7 , 3.2)	1.9 (1.3 , 2.9)	1.5 (1 , 2.3)	1.2 (0.8 , 1.8)
Wrist fracture				
Women	1.6 (1.1 , 2.4)	1.2 (0.8 , 1.8)	1.5 (0.9 , 2.5)	2 (0.8 , 5.2)
Men	1.1 (0.5 , 2.6)	0.6 (0.3 , 1.3)	0.4 (0 , 3.6)	2.5 (0.3 , 24.6)

Note: The hazard ratios were computed per standard deviation reduction in femoral neck bone mineral density (0.14 g/cm^2)

Table 3: Proportion of fractures attributable to osteoporotic BMD and advancing age

Osteoporotic BMD[1]	Age ≥70	Prevalence	Population attributable risk (%)			
			Total fracture	Hip fracture	Vertebral fracture	Wrist fracture
Women						
No	No	0.56	0	0	0	0
No	Yes	0.23	8.5	12.3	9.3	7.0
Yes	No	0.07	5.6	6.5	6.3	3.1
Yes	Yes	0.14	19.4	43.7	19.0	2.1
Total (women)			33.6	62.6	34.7	12.2
Men						
No	No	0.57	0	0	0	0
No	Yes	0.32	16.8	28.4	11.5	0.1
Yes	No	0.04	4.6	7.5	5.4	0.2
Yes	Yes	0.06	13.6	19.8	13.9	0.0
Total (men)			35.1	55.7	30.8	0.2

[1]Osteoporotic BMD: T-score ≤ -2.5;

Table 4: Proportion of mortality attributable to osteoporotic BMD and fracture: a heuristic analysis

	Age	Osteoporotic BMD*	Fracture	Prevalence	RR	Population attributable risk
Women	<70	No	No	0.45	1	0
	<70	No	Yes	0.11	2.56	5.5
	<70	Yes	No	0.04	1.55	2.0
	<70	Yes	Yes	0.03	3.73	3.8
	≥70	No	No	0.15	3.33	26.7
	≥70	No	Yes	0.08	5.04	14.0
	≥70	Yes	No	0.07	5.00	25.1
	≥70	Yes	Yes	0.07	7.75	22.1
Men	<70	No	No	0.52	1	0
	<70	No	Yes	0.06	2.32	0.6
	<70	Yes	No	0.03	1.11	0.3
	<70	Yes	Yes	0.01	2.95	1.7
	≥70	No	No	0.25	2.54	38.8
	≥70	No	Yes	0.07	6.19	9.1
	≥70	Yes	No	0.04	3.40	8.8
	≥70	Yes	Yes	0.03	7.42	6.4

*Osteoporotic BMD: T-score ≤ -2.5; RR: relative risk.

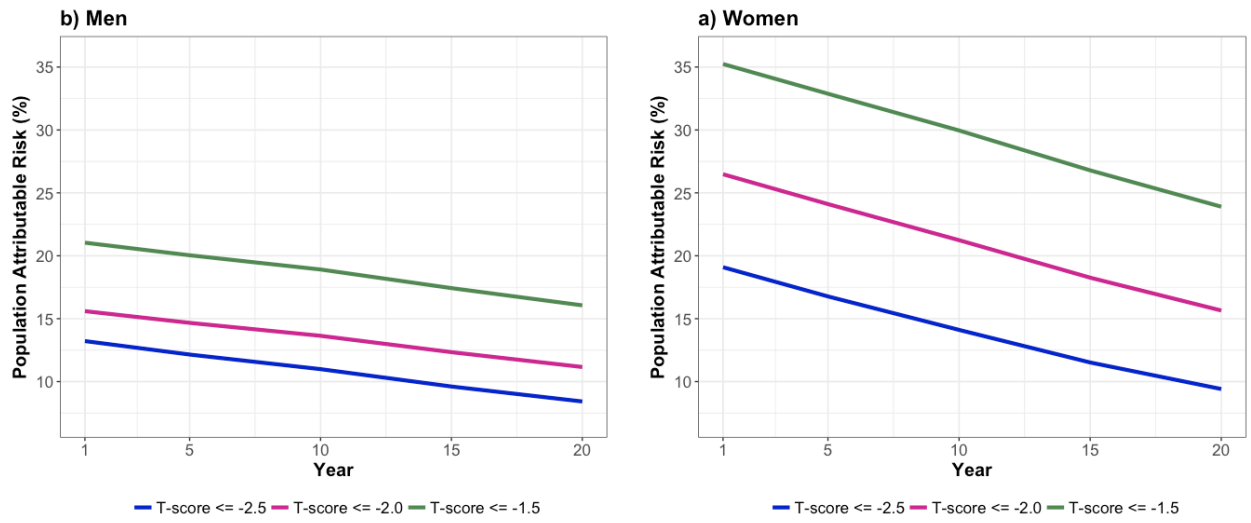

Figure 1: Population attributable fraction of fracture by different thresholds of bone mineral density for men (left panel) and women (right panel).

Appendix I: Table 1. Incidence of fracture by age, "low bone mineral density" status and prior fracture

	Any fracture	Hip fracture	Vertebral fracture	Wrist fracture
Women				
Total	864	188	416	92
Age				
≤ 65	285 (33)	40 (21.3)	135 (32.5)	32 (34.8)
≤ 75	680 (78.7)	122 (64.9)	330 (79.3)	78 (84.8)
≤ 85	835 (96.6)	176 (93.6)	409 (98.3)	91 (98.9)
Low BMD				
≤ −2.5	230 (26.6)	93 (49.5)	133 (32)	19 (20.7)
≤ −2.0	412 (47.7)	126 (67)	209 (50.2)	43 (46.7)
≤ −1.5	580 (67.1)	154 (81.9)	288 (69.2)	61 (66.3)
Prior fracture				
Yes	79 (9.1)	23 (12.2)	32 (7.7)	5 (5.4)
Men				
Total	273	62	129	13
Age				
≤ 65	69 (8)	14 (7.4)	30 (7.2)	9 (9.8)
≤ 75	218 (25.2)	47 (25)	105 (25.2)	12 (13)
≤ 85	267 (30.9)	59 (31.4)	128 (30.8)	13 (14.1)
Low BMD				

≤ −2.5	51 (5.9)	16 (8.5)	27 (6.5)	2 (2.2)
≤ −2.0	80 (9.3)	26 (13.8)	41 (9.9)	3 (3.3)
≤ −1.5	117 (13.5)	38 (20.2)	60 (14.4)	4 (4.3)
Prior fracture				
Yes	28 (3.2)	7 (3.7)	19 (4.6)	3 (3.3)

Numbers are the actual number of fracture and percentage of total in bracket.

Appendix Table 2. Attributable fraction of fractures to low bone mineral density in men and women (T-scores ≤ -2.5)

Time	**1 year**	**5 year**	**10 year**	**15 year**	**20 year**
Any fracture					
Women	19.1	16.8	14.1	11.5	9.4
Men	13.2	12.1	11	9.6	8.4
Hip fracture					
Women	41.3	40.0	38.0	36.1	32.2
Men	22.2	21.8	21.2	19.7	18.4
Vertebral fracture					
Women	21.8	21.0	19.7	17.8	15.8
Men	14.3	13.8	13.3	12.4	11.8
Wrist fracture					
Women	NA	NA	NA	NA	NA
Men	11.4	11.3	11.3	11.3	11.3

Note: The attributable fraction was adjusted for age and BMI; NA: not estimated due to non-statistically significant association between BMD and fracture risk.