Original Article

Risk of subsequent fractures and mortality in elderly women and men with fragility fractures with and without osteoporotic bone density: The Dubbo Osteoporosis Epidemiology Study†

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Initial Date Submitted September 4, 2014; Date Revision Submitted October 15, 2014; Date Final Disposition Set October 24, 2014

Journal of Bone and Mineral Research

DOI 10.1002/jbmr.2393

Abstract

Context Half of fragility fractures occur in individuals with non-osteoporotic BMD (BMD T-score >-2.5), however there is no information on post-fracture adverse events of subsequent fracture and mortality for different BMD levels.

Objectives: To determine the risk and predictors of subsequent fracture and excess mortality following initial fracture according to BMD.

Design: Community dwelling participants aged 60+ from Dubbo Osteoporosis Epidemiology Study with incident fractures followed from1989-2011.

Outcome measurements: Risk of subsequent fracture and mortality according to BMD categorised as normal (T-score <-1), osteopenia (T-score≤ -1 and > -2.5) and osteoporosis (T-score ≤-2.5).

Results: There were 528 low-trauma fractures in women and 187 in men. Of these, 12% occurred in individuals with normal BMD (38 women, 50 men) and 42% in individuals with osteopenia (221 women, 76 men). The RR of subsequent fracture was >2.0 fold for all levels of BMD (normal BMD: 2.0 (1.2- 3.3) for women and 2.1 (1.2- 3.8) for men, osteopenia: 2.1 (1.7- 2.6) for women and 2.5 (1.6- 4.1) for men and osteoporosis 3.2 (2.7- 3.9) for women and 2.1 (1.4- 3.1) for men. The likelihood of falling and reduced quadriceps strength contributed to subsequent fracture risk in women with normal BMD. By contrast with subsequent fracture risk, post-fracture mortality was increased particularly in individuals with low BMD [age-adjusted SMR for osteopenia 1.3 (1.1- 1.7) and 2.2 (1.7- 2.9) for women and men, respectively and osteoporosis 1.7 (1.5- 2.0) and 2.7 (2,0- 3.6) for women and men, respectively].

Conclusion: This study demonstrates the high burden of subsequent fracture in individuals with normal BMD and osteopenia, and excess mortality particularly for those with osteopenia (and osteoporosis). These findings highlight the importance of these fractures and underscore the gap in evidence for benefit of anti-osteoporotic treatment for fragility fracture, in those with only mildly low BMD.

Keywords: Osteoporosis < DISEASES AND DISORDERS OF/RELATED TO BONE, General population studies < EPIDEMIOLOGY, Fracture prevention < PRACTICE/POLICY-RELATED ISSUES

Introduction

Low BMD is considered the most important determinant of fracture risk. However, over half of all low-trauma fractures occur in people with non-osteoporotic BMD (BMD T-score>-2.5) [1-4]. The occurrence of a low trauma fracture in the elderly is associated with an increased risk of subsequent fracture and premature mortality [5-9]. However, it is not clear whether these long-term post-fracture outcomes vary according to level of BMD and in particular differ for those individuals with a fragility fracture without osteoporotic BMD.

The relationship between BMD measurement and fracture risk has been thoroughly investigated [10-12]. In a meta-analysis, fracture risk increased by 1.5- 3.0- fold with each SD decrease in BMD measured at lumbar spine or hip, respectively [10]. In that meta-analysis the predictive ability of 1 SD lower bone mass was similar to that for 1 SD increase in blood pressure for stroke and 1 SD higher serum cholesterol concentration for cardio-vascular diseases outcomes. However, despite this high specificity, BMD measurement has a relatively poor sensitivity, meaning that there is a significant overlap of BMD values between fracture and control cases. Indeed, several osteoporosis epidemiological studies have reported that approximately half of the fractures occur in individuals with non-osteoporotic BMD [1, 4], and this proportion is even higher, >70%, in men [13].

It is well documented that a history of a minimal trauma fracture increases the risk of a subsequent fracture [5, 14, 15]. However, the role of BMD in the prediction of subsequent fracture risk is less clear. In one meta-analysis, the risk of a subsequent fracture was increased 1.86- fold by a prevalent fracture. Interestingly, this relative risk was only marginally decreased by taking BMD into account in both women and men [14]. Furthermore, although, increased subsequent fracture risk following initial fracture is well documented, there are no data on the risk or determinants of subsequent fracture in individuals without osteoporotic BMD.

Premature mortality has been reported not only following hip fracture [16], but also following vertebral [17] and other major fragility fractures [6, 7], however, its cause is unclear. Low bone mass, on the other hand, has been found to be associated with all cause and cardio-vascular mortality in both women and men, independent of osteoporotic fractures. One meta-analysis reported a modest but significant increase of ~13-17 % risk of all cause and cardio-vascular mortality per SD decrease in femoral neck BMD in the general population [18]. However, the effect of BMD on mortality does not seem to be linear such that, although low BMD was consistently found to be associated with high mortality, normal BMD was not associated with better survival [19]. Thus, it is unclear whether individuals with fragility fracture but without osteoporotic BMD have increased post-fracture associated mortality.

The specific aims of this study were to ascertain the risk and predictors of poor outcomes of subsequent fracture and premature mortality following initial fracture according to different levels of bone mineral density in a cohort of women and men from the Dubbo Osteoporosis Epidemiology Study.

Methods

Study Population, Setting and Design

The study population consisted of women and men over the age of 60 with incident osteoporotic fractures enrolled in the Dubbo Osteoporosis Epidemiology Study. The aims, methodology and protocols for this study have been described previously [5, 8]. Briefly, this ongoing prospective study, started in April 1989, has recruited over 60% of the eligible 60+ population. Dubbo is a semiurban city of 32,000 people, with a relatively stable population that has its own radiological services. This permitted the identification and record of virtually all fractures occurring in the community, thus constituting an ideal setting for the purpose of this epidemiological study. This study was approved by the St Vincent's Hospital Human Research Committee. After signing the informed consent form, participants attended regular ~ 2-3 yearly clinic visits for data collection and measurements.

The characteristics of the fracture cohort have been previously described [5, 8]. The current study included only individuals who sustained at least one low-trauma fracture and who had a clinical visit around the date of the initial fracture, so that a bone density assessment reasonably close to the fracture event could be obtained. This visit was selected to be either within 5 years prior to the fracture, or within 2 years post-fracture. When 2 visits (one prior and one post-fracture) met the criteria, the visit prior to the fracture was selected. Thus, from the whole fracture cohort, 528 women (55 %) and 187 men (54%) were selected. They had similar age, gender and fracture type distribution to the whole fracture cohort.

Assessment of outcomes and risk factors

Fracture ascertainment

All fracture events occurring from April 1989 onwards were identified through the two and at times three radiological services in Dubbo as previously recorded. Circumstances of the fracture were obtained through direct interview. Only minimal trauma fractures (following a fall from standing height or less) were included. High trauma fractures, pathological fractures (e.g. cancer, Paget's disease) as well as fractures of the head, fingers and toes were excluded. Fractures were also classified according to initial fracture type: hip, vertebral and non-hip non-vertebral fracture.

Data measurements *BMD measurements:* BMD (g/cm^2) was measured at the site of femoral neck by DXA using a GE LUNAR Densitometer (Madison, WI). The coefficient of reliability at our institution was 0.96 at the site of femoral neck for the normal subjects. BMD was analysed either as a continuous variable or in 3 categories: normal BMD, osteopenia and osteoporosis, based on T-score. Individuals who had a T-score of 2.5 SD or more below the young adult reference population were classified as "osteoporotic", those with a T-score between 2.5 and 1.0 below were classified as "osteopenic" and a T-score above -1.0 as "normal BMD".

Clinical data: Information on co-morbidities, medical history and falls were collected through direct interview by a study co-ordinator. Co-morbidities were analysed according to five major categories: cardio-vascular, respiratory, neurological, diabetes and cancer. Falls were analysed according to fall history in the year prior to the clinic visit around the first fracture date (no falls/ at least 1 fall/≥ 2 falls) or total number of falls in an interval defined as between 5 years prior to and 1 year post-fracture).

Mortality data
Mortality status was ascertained continuously during the study follow-up through systematic searches of funeral director lists, local newspapers, and Dubbo media reports. Deaths were verified from the New South Wales Registry of Births, Deaths, and Marriages.

Statistical Analysis
Estimates of subsequent fracture and mortality rates according to categorical BMD
For this analysis participants were classified according to gender-specific BMD level into 3 groups: normal BMD, osteopenia, and osteoporosis. The analysis was performed initially for all fracture types and then stratified by initial fracture type (hip, vertebral and non-hip non-vertebral fracture). Women and men were analysed separately.

The incidence of subsequent fracture was calculated as the number of subsequent fractures per 1000 person-years of follow-up, assuming a Poisson distribution. Follow-up time was calculated from the first low-trauma fracture to second low-trauma fracture or death, or end of the study (1 January 2012). Relative risk of subsequent fracture was calculated as the ratio of subsequent fracture rate to the population's initial fracture rate. The calculation of initial fracture rate has been described in detail previously [5].

Similar to subsequent fracture, the incidence of mortality was calculated as the number of deaths per 100 person-years of follow-up, assuming the occurrence of death followed a Poisson distribution. The time to follow-up used for the calculation of person-years was calculated for each participant from the date of initial fracture to death or end of study (1 January 2012). Age -standardized mortality ratios were obtained using the Dubbo general population mortality rates observed during the study period [8].

Estimates of subsequent fracture and mortality risk according to continuous BMD
Cox Proportional hazards models were used to assess the effect of BMD on subsequent fracture and mortality rates. Two age-adjusted Cox proportional hazards models were fitted according to the 2 outcomes of subsequent fracture and mortality. Subsequent fracture rates were compared to initial fracture rates according to BMD level, while mortality rates were compared to general population mortality (Figure 3). The general population mortality estimates used in this analysis were based on the 5-year Dubbo population mortality and the median T-score, obtained from the BMD reports for each age group and gender analysed (60-74: -1.4 and -1.0 for women and men, respectively, and 75+: -2.1 and -1.4 for women and men respectively). The mortality curve for the general population was then estimated using this median T-score as the flexion point with the slope per SD obtained from the regression model.

Predictors of subsequent fracture
Risk factors for subsequent fracture were obtained using Cox Proportional Hazards Models. In order to examine the risk of subsequent fracture in fragility fractures without osteoporotic BMD, additional survival models were performed in the group of people with normal BMD and osteopenia. Variables analysed included age at initial fracture, falls (yes/no), frequency of falls (number of falls/year), quadriceps strength and sway. Independent predictors of subsequent fracture and mortality were

obtained using the stepwise regression method and then confirmed using the Akaike Information Criterion (AIC).

Population attributable risk (PAR) of subsequent fracture and mortality
PAR was used to determine the contribution of fragility fractures without osteoporotic BMD to the total population burden of subsequent fractures and deaths following fracture.
All statistical analysis was performed using SAS, version 9.

Results
There were 528 women and 187 men with incident fractures, who had a visit around the initial minimal trauma fracture. The average interval between clinical visit and fracture was 8 months (IQR: 21 months prior to fracture - 2 months post-fracture) for women and 6 months (IQR: 17 months prior fracture - 3 months post-fracture) for men. Women and men had a similar distribution of fracture type [hip fracture (13-17%), vertebral fracture (31-32%) and non-hip non-vertebral fracture (51-56%)], similar number and type of co-morbidities, and similar age at fracture (Table 1). Women reported more falls and had on average lower quadriceps strength than men.

Over, half of the individuals with fragility fracture had a non-osteoporotic bone mineral density (12% normal BMD and 42% osteopenia). The proportion of these non-osteoporotic fragility fractures was higher in men than women (68% vs. 49%; $p<0.00001$) (Table1, Figure 1).

Risk of subsequent fracture according to BMD
During the study follow-up [mean 9.5 years (IQR: 5.2- 14.6) for women and 6.4 years (IQR: 2.2- 11.6) for men], 251 women and 55 men had a subsequent fracture (Figure 1). Interestingly, 45% of these subsequent fractures occurred in individuals with non-osteoporotic BMD.

Both initial and subsequent fracture rates increased continuously with decreasing femoral neck T-score, in both women and men (Figure 2). Initial fracture rate was low (<20%) for 'non-osteoporotic" levels of BMD and increased exponentially with a decreasing BMD. However, subsequent fracture rates were higher than initial fracture rates for every given T-score, in both genders. For women, subsequent fracture risk was elevated for all levels of BMD in both age groups. Thus, even a T-score of 0 for older women or -1 for younger women was associated with a subsequent fracture risk >20%. Similarly for men, a 20% subsequent fracture risk occurred for a bone density T-score around -1.

Age-adjusted relative risk of subsequent fracture according to BMD levels and fracture type
Consistent with the above analysis, age-adjusted RR of subsequent fracture was elevated for all levels of BMD in both women and men (Table 2). For women, the risk of subsequent fracture was highest for those with osteoporosis [age-adjusted RR: 3.2 (95% CI, 2.7- 3.9)] but was still elevated ~2-fold for those with osteopenia [age-adjusted RR: 2.1 (95% CI, 1.7- 2.6)] and normal BMD [age-adjusted RR: 2.0 (95% CI, 1.2- 3.3)]. For men, the risk of subsequent fracture was ~ 2-fold higher than the risk of initial fracture and was similar for all levels of BMD [age adjusted RR; 2.1

(95% CI, 1.2- 3.8) for those with normal BMD, 2.5 (95% CI, 1.6- 4.1) for osteopenia and 2.1 (95% CI, 1.4- 3.1) for osteoporosis].

However, this risk varied according to the initial fracture type. Perhaps not surprisingly, individuals with hip fracture had predominantly lower bone mass (71% osteoporosis and 29% osteopenia). The risk of subsequent fracture was high for those with osteoporosis [women: 2.9 (95% CI, 2.0- 4.3) and men: 7.4 (95%, 3.0- 18)] and for women with osteopenia [women: 4.5 (95% CI, 2.3-9.1)]. The risk of subsequent fracture in men with osteopenia was not significantly increased, possibly masked by the high mortality (77%) in this relatively small group (n=13) (Table 2).

In contrast to hip fractures, over half of the individuals with clinical vertebral fracture had "non-osteoporotic BMD" (10% normal BMD and 42% osteopenia). For women the risk of subsequent fracture was significantly elevated for all levels of BMD and ranged between 2.4 and 3.8. For men, the risk of subsequent fracture was also elevated for all levels of BMD, although this was not significant for those with normal BMD (Table 2).

Similar to vertebral fractures, the majority of individuals with non-hip non-vertebral fractures had higher bone mass (16% normal BMD and 45% osteopenia). For women, the risk of subsequent fracture was elevated for those with osteopenia and osteoporosis, but not normal BMD, while for men the risk was elevated across all levels of BMD (Table 2).

Predictors of subsequent fracture risk

Several risk factors such as age at initial fracture, quadriceps strength, sway and propensity to fall as well as total number of falls were examined in order to determine whether they play a role in subsequent fracture risk. Not surprisingly, low BMD was the strongest predictor of subsequent fracture risk in both women and men. A decrease in femoral neck BMD by 1 SD (0.12 g/cm^2) was associated with 35-62% increased risk of future fracture in both women and men [adjusted HR 1.35 (1.18-1.55) in women and 1.62 (1.33-1.98) in men)] after adjusting for age.

In an effort to define risk factors for subsequent fracture in individuals with non-osteoporotic fractures, two additional multivariable survivals models were performed for normal BMD and osteopenia. In the small group of women with normal BMD (n=40), a greater number of falls and a decrease in quadriceps strength by 1 SD (7.9 kg) were associated with over 2-fold risk of subsequent fracture [falls: HR 2.85 (95% CI, 1.12- 7.22); p=0.03 and quadriceps strength 2.39 (95% CI, 1.20- 4.80); p=0.02]. No additional subsequent fracture risk factors were identified in men with normal BMD, or in women and men with osteopenia.

Post-fracture mortality according to BMD

During the study follow-up, 245 women and 114 men died. Similar to subsequent fracture risk, mortality increased with lower femoral neck T-score (Figure 3). For women and men, post-fracture mortality rates increased exponentially with decreasing femoral neck T-score. However, it only diverged from the population mortality rates for a T-score in the osteoporotic range. In men, there appeared to be a greater effect of fracture on mortality than in women, as previously observed [5].

The age-adjusted SMRs confirmed the increased mortality, particularly for the lower bone density levels. For women, standardized mortality ratios ranged from 1.7- 2.2 fold [osteoporosis: 1.7 (95% CI, 1.5- 2.0), osteopenia 1.3 (95% CI, 1.1- 1.7) and normal BMD: 2.2 (95% CI, 1.3- 3.5)]. For men, standardized mortality ratios was slightly higher than for women for osteoporosis [2.7 (95% CI, 2.0- 3.6)] and osteopenia [2.2 (95% CI, 1.7- 2.9)] but not normal BMD [1.2 (95% CI, 0.8- 1.9)]. The increased mortality observed in women with normal BMD was largely driven by high mortality after non-hip non-vertebral fractures (Table 3).

In general, the risk of deaths was highest for hip, followed by vertebral and non-hip non-vertebral fractures with a lower BMD conferring a additional higher associated mortality. However, in this sub-analysis, the numbers of individual events within each fracture group and BMD category were low limiting the reliability of the findings.

Population attributable risk (PAR) for subsequent fracture and mortality
Approximately 5-23 % of both subsequent fracture and mortality could be attributed to initial fractures with normal BMD level (Table 4).

Given the high number of fragility fractures with osteopenic BMD >30% of subsequent fractures and 11% of deaths in women, and 50% of subsequent fractures and >30% of deaths in men could be attributed to this group of fractures.

Discussion
This study reports the high incidence of subsequent fracture and mortality in individuals with normal or osteopenic BMD at the time of the initial fragility fracture. The majority of the individuals with incident fragility fractures had "non-osteoporotic" BMD at the time of their initial fracture. The prevalence of osteopenia and normal BMD was higher for clinical vertebral fracture and non-hip non-vertebral than hip fractures and was also higher in men than women. This was despite using gender specific young normal ranges. If, as has been proposed, young normal female values should be used to estimate men's T-scores, this would exaggerate this discrepancy. However, more importantly over 40% of the post-fracture events of subsequent fracture and deaths in this cohort occurred in individuals with "non-osteoporotic BMD". There are currently few data for efficacy of anti-osteoporotic treatments in those with a T-score >-2.0. Hence these findings suggest that clinical trials are essential in this group to see if subsequent fractures can be averted.

Fragility fractures have been previously linked to increased risk of subsequent fracture and mortality in previous studies including our own. The risk of subsequent fracture has been extensively researched, albeit mostly in women and has been predominantly observed in the first 5-years post-fracture [8, 20]. Various risk factors have been found to be associated with this increased risk, including low BMD. However, the risk of subsequent fracture according to different levels of BMD, which is the main focus of this paper, has not been previously reported and neither has the risk of mortality in this context.

BMD is currently widely used for fracture risk prediction. However, BMD sensitivity for fracture prediction is limited, in that a large proportion of total fragility fractures occur in individuals with non-osteoporotic bone density [10]. The prevalence of

osteopenia and normal BMD amongst individuals with fractures has been reported almost exclusively for women with a similar proportion of high bone mass amongst women with prevalent or incident fracture [2, 3, 21]. By contrast, only one study has reported the prevalence of high bone mass amongst men with fragility fracture; an earlier analysis of the current cohort [13]. In the current study, 12% of the individuals with incident fractures had normal BMD (7% women and 27% men) and 42% had osteopenia (42% women and 41% men). All fracture types contributed equally to the group with osteopenia, while the group with normal BMD was composed predominantly of clinical vertebral and non-hip non-vertebral fractures.

Despite a relatively good awareness of the limited sensitivity of BMD for fracture risk prediction, and high prevalence of normal BMD and osteopenia amongst fracture population, there is a paucity of data on the risk of future fracture for these individuals. There are few epidemiological studies that report subsequent fracture risk in osteopenic women, and even fewer for men [2, 13, 22]. The current study reported not only the high risk of subsequent fracture in individuals with normal and osteopenic BMD but also on breakdown by fracture types and gender. The risk of subsequent fracture was increased by 2-fold in both women and men with non-osteoporotic BMD, including both osteopenic and normal BMD. Interestingly, the subsequent fracture risk was increased for all types of fracture in the group with osteopenia, while in individuals with normal BMD the risk of subsequent fracture was primarily increased following clinical vertebral fractures in women and non-hip non-vertebral fractures in men. No hip fractures had occurred in individuals with normal BMD.

Another interesting finding of this study is the higher prevalence of normal BMD and osteopenia amongst men than women. Although the cause of this discrepancy could not be fully investigated, the bone size differences between women and men may play a role. Areal BMD, a two-dimensional measurement, does not fully account for size, which is a three-dimensional entity. It has been previously proposed that volumetric bone density would overcome this. In a previous study from the same cohort, women and men with hip fractures had similar volumetric BMD, despite women having significant lower areal BMD than men [23].

Most importantly, due to the high prevalence of fragility fracture with non-osteoporotic BMD, up to 23% of all subsequent fractures may be associated with normal BMD and up to 50% with osteopenia. Thus, given the impact non-osteoporotic fractures have on the population burden of subsequent fracture it is important to identify additional risk factors for fracture. It may be possible that the risk of fracture in these individuals depends on the quality of bone that is not captured by DXA-BMD measurements. Several studies have shown that bone turnover markers may play a role in the risk of fractures in individuals with osteopenia [2, 24, 25]. For example in one study, women with high levels of bone alkaline phosphatase had over 2-fold risk of fracture [2].

However, it is important also to define non-bone related factors that may predict subsequent fracture risk in individuals with higher BMD. The role of falls in fracture risk prediction is well recognized [26, 27]. We and more recently, others have reported sway and propensity to fall to be an independent fracture risk factors in women with osteopenia [2]. The findings from our study suggest that falls and muscle

weakness may play a role in the risk of subsequent fracture in women with normal BMD, but not in men. Women, not only reported a higher frequency of falls than men, but those who fell had 2-fold higher risk of subsequent fracture compared to women who did not fall.

Another important finding from this study is that individuals with non-osteoporotic fragility fracture have higher mortality rates than an age-adjusted general population at least in the osteopenic range. This is particularly important as, although osteoporosis has been previously demonstrated to be a predictor of mortality [28, 29], this group of osteopenic fractures has not been perceived to be a high risk group. Thus this finding warrants further attention.

The mechanism of increased risk of subsequent fracture and mortality following fragility fracture is not clear. The cluster of these events in the first 5-year post-fracture, followed by their decline afterwards, suggest that their cause could result from common risk factors that may trigger fracture- subsequent fracture and/or mortality. In the current study, both the rates of subsequent fracture and mortality increased with decreasing BMD. However, interestingly, low BMD was independently associated with mortality but not subsequent fracture. This suggests that low BMD may affect mortality risk through mechanisms not related to the fracture-event. The role of low BMD in cardio-vascular morbidity and mortality has been previously published [18]. Other factors not analysed in this study such as low muscle strength and frailty have also been separately implicated in both fracture and mortality[30].

Currently low BMD is the most commonly used tool in fracture risk prediction and the diagnosis of osteoporosis. However, findings from this study suggest that using primarily a BMD T-score in the osteoporotic range for therapeutic decision making will leave out many individuals at high risk for future fracture and potential premature mortality. Recently, IOF recommended that treatment should be offered to individuals with higher bone mass in the presence of other fracture risk factors [31].

More challenging may be the management of the individuals with high risk of future fracture who have normal BMD. This study suggests that falls may play a role in the risk of subsequent fracture in women with normal BMD but not in men. The role of falls in subsequent fracture risk has been previously described [32]. In a recent study, the combination of bone and fall risk factors provided a better subsequent fracture risk prediction than only bone related factors [32]. However, it remains to be demonstrated whether anti-resorptive agents will also decrease subsequent fracture risk in this group.

This study has many strengths. It has over 20 years of follow-up and a very low rate (<6%) of drop out. This long follow-up also allowed the recording of a large number of events and therefore the possibility of meaningful analyses according to fracture type, gender and different levels of BMD. The relative isolation of the site of the study has facilitated capturing all fracture events and deaths. However, this study has some limitations. The cohort is predominantly Caucasian, therefore the findings from this study may not be generalizable to other ethnic groups. Deaths following fracture were obtained from local death and funeral listings and thus these may have been underestimated. However, this would only have led to an underestimation of the risk of death. Individual fracture types within specific BMD groupings were modest leading to some unreliability around the estimates for post fracture events in the subcategories. The risk of death could be influenced by a large number of factors, however, in this study only bone-related factors were considered.

In summary, this study not only reported the high prevalence (50%) of osteopenia and normal BMD amongst individuals with fragility fractures, but also the total burden of subsequent fracture and premature mortality in these individuals. Women and men with osteopenia had an increased risk of both subsequent fracture and premature mortality. Women and men with normal BMD also had increased subsequent fracture risk but the association with premature mortality was less clear. The propensity to fall seemed to be a predictor of subsequent fracture in women with normal bone density if not in men.

This study has important clinical implications. It suggests that individuals with osteopenia have significant post-fracture consequences with increased subsequent fracture and mortality. For those with normal BMD the findings are less clear but at least suggest increased subsequent fracture risk. Thus, given the large number of fractures involved, there is an imperative to examine the efficacy or otherwise of anti-resorptive drugs in women and men with fractures and non-osteoporotic BMD.

Declaration of competing interests
D.B., D.A and T.V. N. have no competing interests to declare. J.A.E. has consulted for and/or received research funding from Amgen, Decode, Eli Lilly, Merck Sharp and Dohme, Novartis, Sanofi-Aventis, and Servier. J.R.C. has been supported by and/or given educational talks for, Merck Sharp and Dohme,
Amgen, and Sanofi-Aventis.

Funding
This work was supported by the National Health Medical Research Council Australia (NHMRC project ID; DB 1073430, JRC 1008219, DA, TVN, JRC and JAE 1070187). The authors are solely responsible for the contents of this paper, and do not reflect the views of NHMRC Other funding bodies are Osteoporosis Australia-Amgen grant; the Bupa Health Foundation (formerly MBF Foundation); the Ernst Heine Foundation; and untied grants from Amgen, Merck Sharp & Dohme, sanofi-Aventis, Servier, and Novartis.

Role of the Sponsor
The study sponsors had no role in the study design; collection, analysis and interpretation of the data; the writing of this report; or the decision to submit this paper for publication.

Figure legends

Figure 1 Flow chart of Dubbo Osteoporosis Epidemiology Study according to BMD at the time of the initial fragility fracture

Figure 2 5-year initial and subsequent fracture risk according to femoral neck T-score stratified according to age (>75 and ≤ 75 years) and gender (women and men)

Figure 3 5-year mortality rate for fracture and general population according to femoral neck T-score stratified according to age (>75 and ≤ 75 years) and gender (women and men)

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Table 1 Participants characteristics

	Women (n=528)	**Men (n=187)**
Age[1], yrs	77 (7)	77 (7)
Weight[1], kg	63 (12)	75 (13)
Fracture type[2],		
Hip	70 (13)	31 (17)
Vertebral	163 (31)	60 (32)
Non-hip non-vertebral	295 (56)	96 (51)
Femoral neck BMD[1] g/cm^2	0.71 (0.12)	0.83 (0.17)
Femoral neck T-score[2]		
Normal BMD	38 (7)	50 (27)
Osteopenia	221 (42)	76 (41)
Osteoporosis	269 (51)	61 (33)
Falls (yes)[2]	412 (78)	117 (63)
Quadriceps strength[3], kg	18 (13-24)	30 (22-38)
Sway[3], mm^2	628 (204-720)	738 (311-914)
Co-morbidities[2]		
None	169 (32)	70 (37)
1	159 (30)	47 (25)
2	121 (23)	49 (26)
3 or more	79 (15)	21 (11)
Cardio-vascular[2]	133 (25)	52 (28)
Respiratory[2]	55 (10)	23 (12)
Hypertension[2]	251 (48)	58 (31)
Neurological[2]	91 (17)	33 (18)
Cancer[2]	91 (17)	36 (19)

*Normal BMD: Femoral neck T-score>-1; Osteopenia: -1 >Femoral neck T-score>-2.5; Osteoporosis Femoral neck T-score≤-2.5

[1] Values represent means (SD)

[2] Values represent number (%)

[3] Values represent means (interquartile range: 25%-75%)

Table 2 Absolute and relative risk of subsequent fracture according to BMD and initial fracture type

Initial fracture	**Women**			**Men**		
	Subsequent fracture (n)	Subsequent Rates per 1000 person-years (95% CI)	Relative Risk (Subsequent / initial fracture) (95 % CI)	Subsequent fracture (n)	Subsequent fracture Rates per 1000 person-years (95% CI)	Relative Risk (Subsequent/ Initial fracture) (95 % CI)
All Fractures						
Normal BMD	15	51 (31- 84)	**2.0 (1.2- 3.3)**	12	31 (17- 54)	**2.1 (1.2- 3.8)**
Osteopenia	89	57 (47- 71)	**2.1 (1.7- 2.6)**	18	48 (30- 76)	**2.5 (1.6- 4.1)**
Osteoporosis	147	104 (88- 122)	**3.2 (2.7- 3.9)**	25	55 (37- 81)	**2.1 (1.4- 3.1)**
Hip						
Normal BMD	-	-	-	-	-	-
Osteopenia	8	133 (67-266)	**4.5 (2.3- 9.1)**	2	39 (10-156)	**2.2 (0.5- 8.8)**
Osteoporosis	26	103 (70-151)	**2.9 (2.0- 4.3)**	5	157 (65-378)	**7.4 (3.0-18)**
Vertebral						
Normal BMD	5	72 (30-172)	**2.7 (1.1- 6.4)**	2	39 (10-156)	**2.2 (0.6- 9.0)**
Osteopenia	26	70 (48-103)	**2.4 (1.6- 3.6)**	7	88 (42-185)	**4.2 (2.0-8.9)**
Osteoporosis	43	127 (94-172)	**3.8 (2.8- 5.2)**	12	121 (68-212)	**7.4 (4.1- 13.1)**
NHNV						
Normal BMD	10	44 (24-82)	1.8 (0.9- 3.3)	10	31 (17-58)	**2.2 (1.2- 4.2)**
Osteopenia	55	49 (38- 64)	**1.9 (1.4- 2.4)**	9	38 (20-73)	**2.4 (1.3- 4.7)**
Osteoporosis	78	94 (75- 118)	**3.1 (2.5- 3.9)**	8	79 (39- 158)	**5.3 (2.6- 10.7)**

Table 3 Absolute mortality rates and age-adjusted standardized mortality ratios according to BMD and initial fracture type

Initial fracture	Women			Men		
	Death (n)	Mortality Rates per 100 person-years (95% CI)	SMR (95% CI)	Death (n)	Mortality Rates per 100 person-years (95% CI)	SMR (95% CI)
All Fractures						
Normal BMD	17	47 (29- 76)	**2.2 (1.3- 3.5)**	20	44 (29- 69)	1.2 (0.8- 1.9)
Osteopenia	76	38 (30- 47)	**1.3 (1.1- 1.7)**	50	118 (90- 156)	**2.2 (1.7- 2.9)**
Osteoporosis	152	76 (64- 89)	**1.7 (1.5- 2.0)**	44	137 (102-184)	**2.7 (2.0- 3.6)**
Hip						
Normal BMD	-	-	-	1	49 (7- 349)	1.1 (0.2- 7.9)
Osteopenia	12	120 (68- 210)	**3.0 (1.7- 5.3)**	10	165 (89- 306)	**2.9 (1.6- 5.5)**
Osteoporosis	36	101 (73- 140)	**1.9 (1.4- 2.7)**	14	361 (214-610)	**5.1 (3.0- 8.6)**
Vertebral						
Normal BMD	4	46 (17- 123)	1.8 (0.7- 4.7)	6	113 (51- 251)	2.0 (0.9- 4.5)
Osteopenia	21	43 (28- 66)	1.2 (0.8- 1.8)	15	151 (91- 250)	**2.0 (1.2- 3.2)**
Osteoporosis	47	90 (68- 120)	**2.0 (1.5- 2.6)**	20	141 (91- 218)	**2.8 (1.8- 4.4)**
NHNV						
Normal BMD	13	47 (27- 81)	**2.3 (1.3- 4.0)**	13	35 (20- 59)	1.0 (0.6- 1.7)
Osteopenia	43	30 (22- 41)	1.2 (0.9- 1.6)	25	95 (64- 141)	**2.2 (1.5- 3.2)**
Osteoporosis	69	61 (48- 77)	**1.5 (1.2- 1.9)**	10	72 (38- 133)	1.5 (0.8- 2.8)

Table 4 Population attributable risk of subsequent fracture and mortality according to BMDF and initial fracture type

Fracture Type	Femoral neck BMD T-score	Prevalence	PAR Re-fracture	PAR Mortality
Women				
All Fractures	Normal	0.06	0.07	0.07
	Osteopenia	0.42	0.32	0.11
	Osteoporosis	0.51	0.53	0.26
Men				
All Fractures	Normal	0.27	0.23	0.05
	Osteopenia	0.41	0.38	0.33
	Osteoporosis	0.32	0.26	0.35

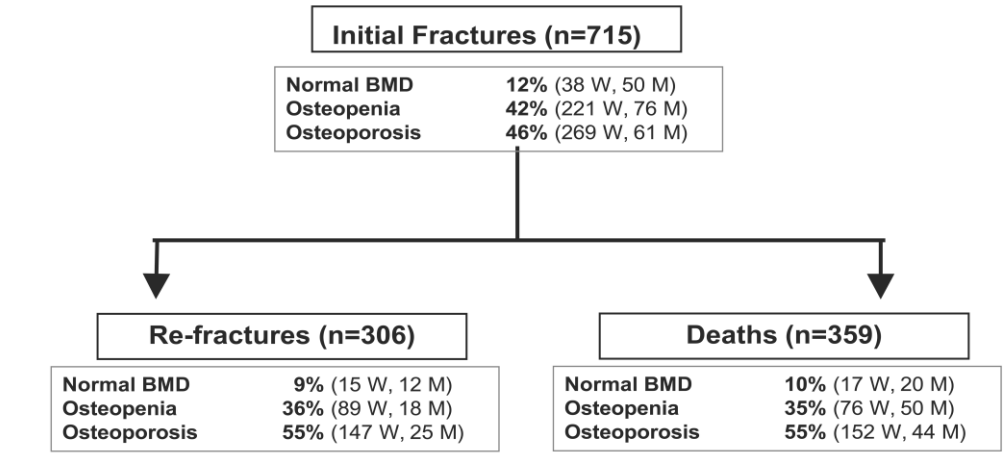

Figure 1

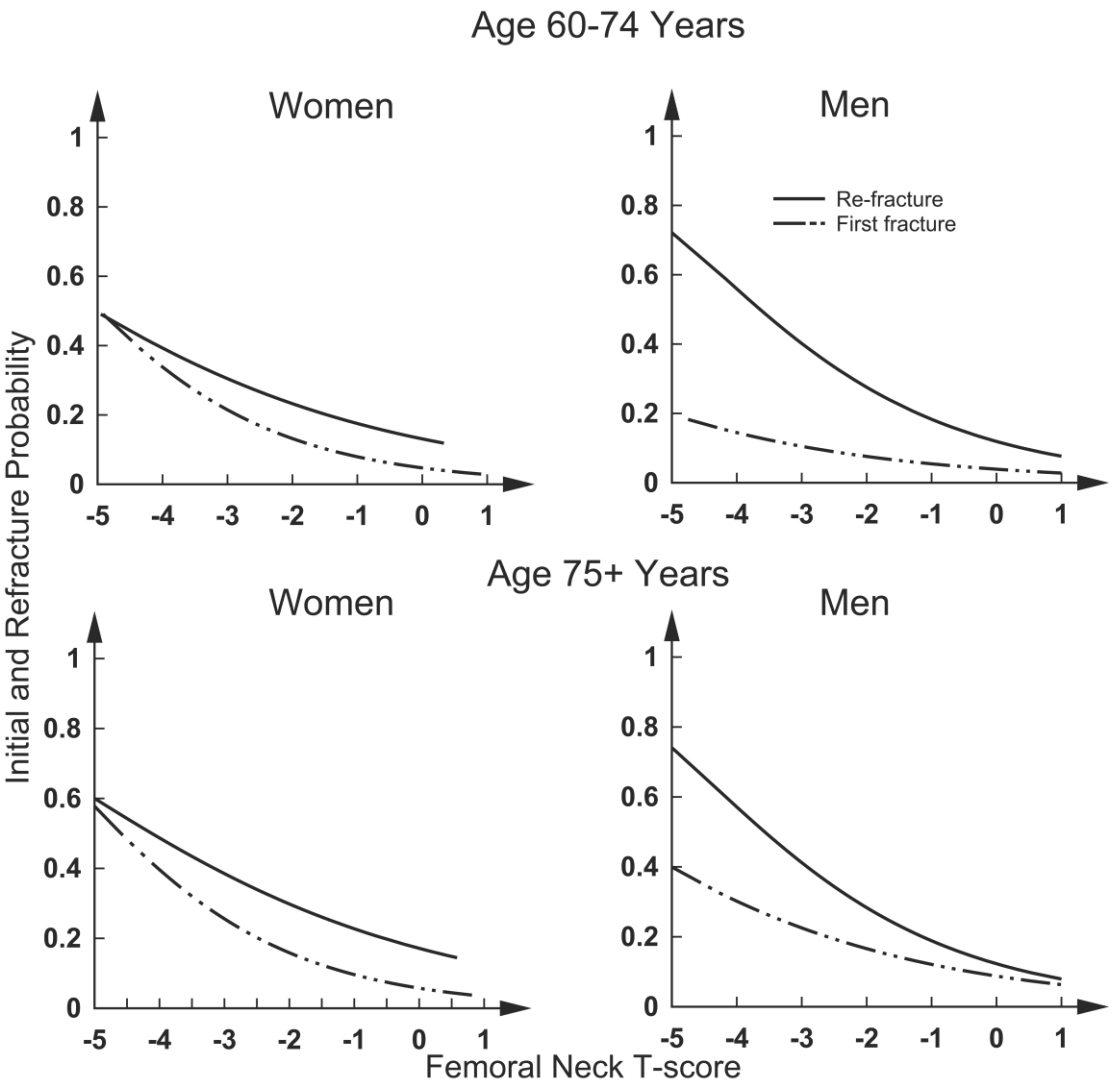

Figure 2

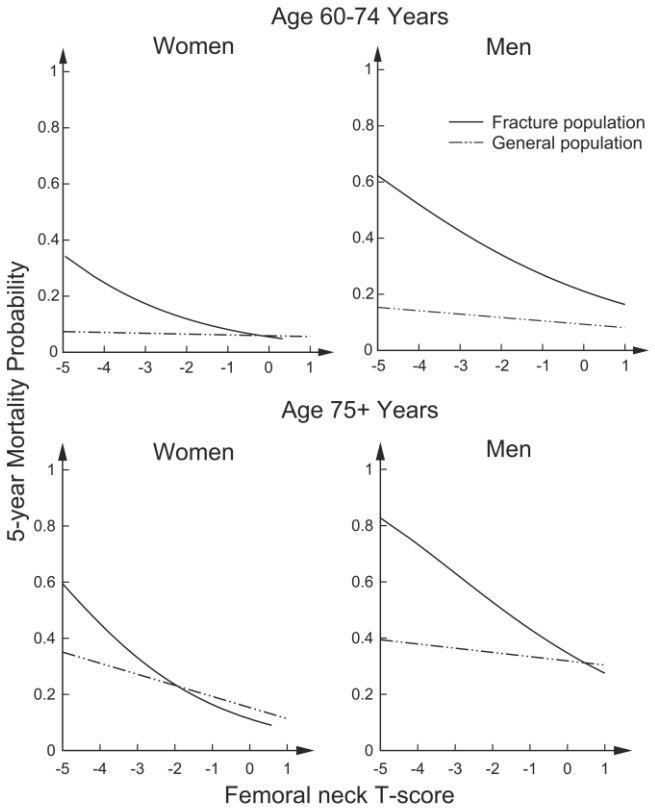

Figure 3