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Repeat Bone Mineral Density Screening Measurement and Fracture Prediction in Older Men: A Prospective Cohort Study

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Abstract

Context: Whether repeated bone mineral density (BMD) screening improves fracture prediction in men is uncertain.

Objective: We evaluated whether a second BMD 7 years after the initial BMD improves fracture prediction in older men.

Methods: Among 3651 community-dwelling men (mean age 79.1 years) with total hip BMD at baseline and Year 7 (Y7), self-reported fractures after Y7 were confirmed by radiographic reports. Fracture prediction assessed using Cox proportional hazards regression and logistic regression with receiver operating characteristic curves for models based on initial BMD, BMD change, and the combination of initial BMD and BMD change (combination model).

Results: During an average follow-up of 8.2 years after Y7, 793 men experienced ≥ 1 clinical fractures, including 426 men with major osteoporotic fractures (MOF) and 193 men with hip fractures. Both initial BMD and BMD change were associated with risk of fracture outcomes independent of each other, but the association was stronger for initial BMD. For example, the multivariable hazard ratio of MOF in the combination model per 1 SD decrement in BMD was 1.76 (95% CI 1.57-1.98) for initial BMD and 1.19 (95% CI 1.08-1.32) for BMD change. Discrimination of fracture outcomes with initial BMD models was somewhat better than with BMD change models and similar to combination models (AUC value for MOF 0.68 [95% CI 0.66-0.71] for initial BMD model, 0.63 [95% CI 0.61-0.66] for BMD change model, and 0.69 [95% CI 0.66-0.71] for combination model).

Conclusion: Repeating BMD after 7 years did not meaningfully improve fracture prediction at the population level in community-dwelling older men.

Key Words: bone mineral density, fracture risk, older men

Abbreviations: AUC, area under the curve; BMD, bone mineral density; BMI, body mass index; DXA, dual-energy x-ray absorptiometry; HR, hazard ratio; MOF, major osteoporotic fracture; MrOS, Osteoporotic Fractures in Men (study); ROC, receiver operating characteristics curve; Y7, Year 7.

The majority of osteoporosis-related fractures in men occur in those men aged 65 years and older (1). Low bone mineral density (BMD) is a strong independent risk factor for fractures in older men (2, 3). Thus, several professional societies (4-6) have recommended osteoporosis screening with initial BMD testing in men aged 70 years or older. However, these guidelines have not addressed the timing of re-screening with repeat BMD measurement as it is uncertain whether repeated BMD testing improves fracture prediction in older men above and beyond that provided by an initial BMD. Previous studies in older (7) and early and late postmenopausal women (8) reported little additional value of repeat BMD 3 to 8 years after the initial BMD in the prediction of incident fractures. Similarly, a second BMD 4 years after the initial BMD did not

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meaningfully improve the prediction of hip or major osteoporotic fracture (MOF) in a study of 802 older adults that included 310 men (9).

In contrast, a previous analysis of 4470 older community-dwelling men enrolled in the Osteoporotic Fractures in Men (MrOS) study found that men with accelerated hip bone loss compared with men who maintained hip BMD during a time period of 4.6 years had increased risks of subsequent hip and any nonvertebral fracture (10). However, BMD change in this analysis was estimated with random effects regression models using BMD measurements at 2 to 3 time points and quadratic terms for age. Thus, results may not be applicable to the clinical practice setting where simple linear BMD change is the measure that is readily accessible for clinical decision making. In addition, this investigation did not evaluate the value of adding BMD change to a fracture prediction model based on initial BMD alone in the discrimination of incident fracture outcomes.

To evaluate whether a second BMD 7 years after an initial BMD improves fracture prediction in older community-dwelling men, the present study used data from 3561 participants in the MrOS study with hip BMD measurements at baseline and Year 7 examinations and subsequent follow-up for any clinical fractures, including MOF and hip fracture.

Methods

Participants

A total of 5994 men aged 65 years and older were enrolled from 2000 to 2002 in the MrOS prospective cohort study (11). Men who were unable to walk without the assistance of another person and men with bilateral hip replacements were not eligible for participation. Participants were recruited from population-based listings in 6 regions of the United States (12). The institutional review board at each participating institution approved the study protocol and written informed consent was obtained from all participants. This analysis was limited to 3561 men who completed hip BMD measurements at both baseline and Year 7 (Y7) examinations (Fig. 1).

Measurement of BMD

BMD at the total hip and femoral neck was measured at baseline and Y7 examinations with dual-energy x-ray absorptiometry (DXA, QDR 4500W, Hologic, Inc., Bedford, MA, USA) using standardized protocols as previously described (13). Extensive quality control procedures were carried out at both examinations, including centralized training and certification of DXA technicians and scanning of a central hip phantom at each clinical center at regular intervals. The coefficient of variation at the total hip for the individual MrOS DXA scanners ranged from 0.3% to 0.7% (10). BMD T-scores were calculated using the National Health and Nutrition Examination Survey (NHANES) young female reference database (14).

Fracture Outcomes

Participants in MrOS were contacted every 4 months after the baseline examination to ask about clinical fracture events and ascertain vital status. Over 98% of these follow-up contacts were completed in active surviving participants. Self-reported fractures were confirmed by radiographic reports.

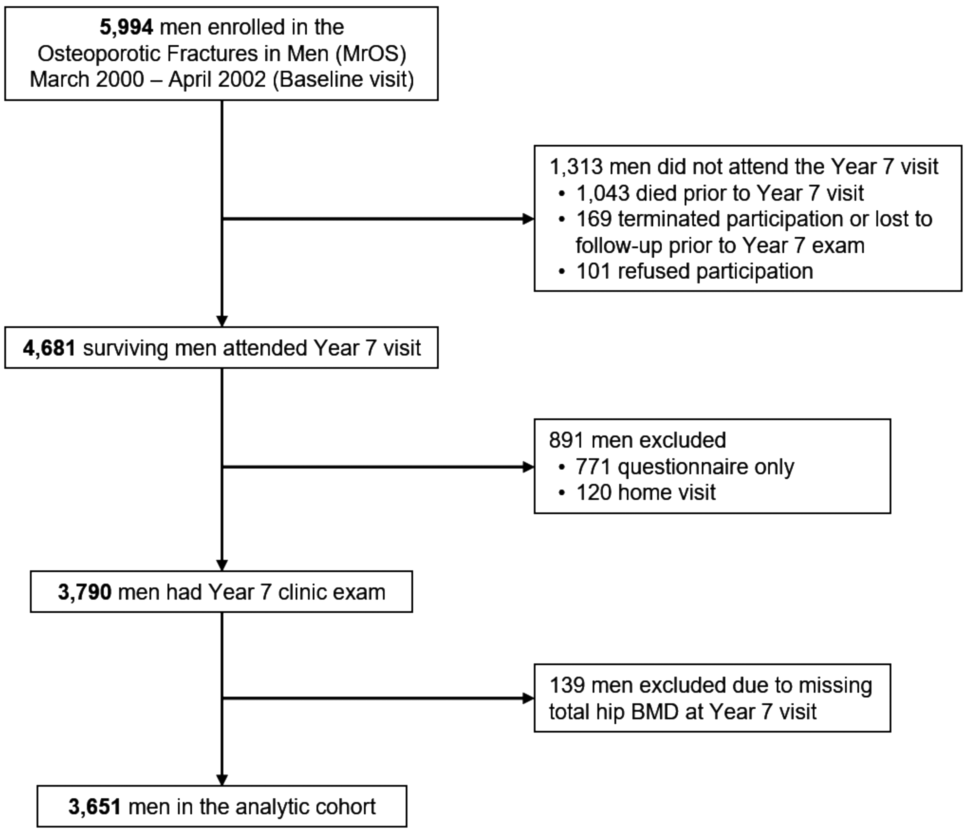

Figure 1. Participant flow diagram.

For any spine fracture that was self-reported, a copy of the community spinal imaging study (x-rays, computed tomography, and/or magnetic resonance imaging) in addition to the radiographic report were obtained. Incident clinical vertebral fractures were confirmed by the study radiologist who used the semiquantitative method of Genant (15) to determine whether the community imaging study showed a new deformity of a higher grade than was present in the same vertebra on study spine films performed at the baseline and Y5 examinations. Deaths were verified with death certificates.

Participants in this analysis were followed up to a maximum of 14.2 years after the Y7 examination to ascertain incident fractures. MOF (hip, clinical vertebral, distal forearm, or shoulder fracture) was the primary outcome of interest (mean [SD] follow-up time to event or censoring 8.7 [4.1] years). Secondary outcomes included any clinical fracture (mean [SD] follow-up time to event or censoring 8.2 [4.2] years) and hip fracture (mean [SD] follow-up time to event or censoring 9.0 [4.0] years).

Other Measures

Date of birth and self-reported race/ethnicity were collected at the baseline examination. A questionnaire that assessed falls in the past year and the history of 12 selected medical conditions (see footnote, Table 1) was completed by participants at the Y7 examination. The number of self-reported medical conditions was summed to calculate a multimorbidity score. Physical activity was assessed using the Physical Activity Scale for the Elderly (PASE) (16).

Body weight (in kg in indoor clothing with shoes removed) was measured with a scale that was calibrated monthly at both the baseline and Y7 examinations. Weight change was calculated by subtracting the baseline weight from the Y7 examination weight and expressed as a percentage of the baseline value (17). Body weight and height (measured in cm with a wall-mounted Harpenden stadiometer that was calibrated every month) were used to calculate body mass index (BMI) at the Y7 examination.

Statistical Analysis

Characteristics of participants with and without incident MOF were compared using chi square tests for categorical variables, ANOVA for continuous variables and Kruskal-Wallis nonparametric tests for skewed variables.

Cox proportional hazards regression was used to calculate the hazard ratio (HR) and 95% CI to estimate the individual associations of initial BMD (per 1 SD decrement) and annualized percent BMD change (per 1 SD decrement) with risk of a given fracture outcome after the Y7 examination. The final model included both initial BMD and BMD change as independent variables. The proportional hazards assumption was verified; there were no violations of proportionality. Initial total hip BMD and annualized percent BMD change at the total hip were the predictors of interest in primary analyses. Models were first unadjusted and then adjusted for age, race/ethnicity, and study enrollment site (base model). On the basis of prior MrOS publications (18-20), associations were subsequently further adjusted for characteristics including prior fracture (confirmed clinical fracture between baseline and Y7 examinations), fall in past year, multimorbidity score, physical activity, BMI, and percentage weight change between baseline and Y7 examination (multivariable model). We performed sensitivity analyses substituting annualized absolute BMD change for annualized percent BMD change at the total hip and substituting BMD measures at the femoral neck for those at the total hip.

While we included men taking osteoporosis drug treatment in the primary analyses, we conducted a sensitivity analysis excluding 336 men taking these medications (bisphosphonates, teriparatide, denosumab) at Y7 or during follow-up. We also performed sensitivity analyses to estimate associations of BMD predictors of interest with fracture outcomes using subdistribution hazards models proposed by Fine and Gray (21) that consider death as a competing risk and calculated subdistribution HRs and 95% CIs.

We made the decision a priori to perform analyses of the association between annualized total hip BMD change (expressed as percent and absolute values) and the fracture outcomes stratified by age group at the repeat BMD measurement (≥ 80 years vs < 80 years), category of initial BMD (T-score ≤ –1.5 at the total hip or femoral neck vs > –1.5) and weight loss 5% or more between the initial and repeat BMD measurement (yes vs no). We tested for an interaction between BMD change and these characteristics for prediction of the fracture outcomes. Based on results of the analyses categorizing initial BMD as T-score ≤ –1.5 vs > –1.5, we performed additional analyses expressing initial BMD as ≤ median value at total hip (0.957 g/cm^2) vs > median value.

Finally, we used unconditional logistic regression with receiver operating characteristic (ROC) curves to compare the performance of models in discriminating men with and without a given incident fracture outcome. We calculated the area under the ROC curve (AUC) for models based on initial total hip BMD alone, annualized percent total hip BMD change alone and the combination of initial total hip BMD and annualized percent total hip BMD change. We compared AUC statistics between models. We also performed analyses stratified by age group, category of initial BMD T-score and weight loss category.

Results

A total of 3651 men with initial hip BMD measurement at the baseline examination and repeat hip BMD measurement at the Y7 examination were included in the analytical cohort. The mean (SD) age of participants was 72.3 (5.1) years at the initial BMD and 79.1 (5.1) years at the repeat BMD. The mean (SD) initial total hip BMD was 0.97 (0.14) g/cm^2 and 683 men (18.7%) had a BMD T-score at the total hip or femoral neck ≤ –1.5. The mean (SD) total hip BMD change was –0.38% (0.75%) or –0.004 (0.007) g/cm^2 per year. Of the 3586 men with an initial BMD T-score at the femoral neck and total hip > –2.5, only 91 (2.5%) transitioned to a BMD T-score of ≤ –2.5 at either skeletal site at the Y7 examination. The correlation coefficient between initial and Y7 total hip BMD was 0.94.

During a mean (SD) follow-up of 8.2 (4.2) years after the Y7 repeat BMD, 793 men (21.7%) experienced 1 or more clinical fractures including 426 men (11.7%) with 1 or more MOF and 193 (5.3%) men with 1 or more hip fractures. Men with vs men without incident MOF were more likely to be White, older, and less active, have experienced a prior confirmed fracture, have reported falling in the past year, and have lower BMI and greater weight loss (Table 1).

Table 1. Characteristics of 3561 men

Characteristic*	Overall (N = 3,651)	With major osteoporotic fracture after Year 7 (N = 426)	Without major osteoporotic fracture after Year 7 (N = 3,225)	*P* value
Age at initial BMD, years, mean (SD)	72.3 (5.1)	73.6 (5.1)	72.2 (5.1)	<0.001
Age at repeat BMD, years, mean (SD)	79.1 (5.2)	80.5 (5.1)	79.0 (5.1)	<0.001
Age ≥ 80 years at repeat BMD, n (%)	1,564 (42.8)	227 (53.3)	1,337 (41.5)	<0.001
White race, n (%)	3,283 (89.9)	397 (93.2)	2,886 (89.5)	0.02
Prior fracture since baseline, n (%)	316 (8.7)	67 (15.7)	249 (7.7)	<0.001
Fall in the past year, n (%)	1,089 (29.8)	155 (36.4)	934 (29.0)	0.002
Multimorbidity score (0-12)†, mean (SD)	1.0 (1.1)	1.0 (1.1)	1.0 (1.1)	0.97
PASE score, mean (SD)	132.0 (68.6)	125.7 (65.7)	132.8 (69.0)	0.04
Body mass index, kg/m^2, mean (SD)	27.1 (3.9)	26.3 (3.8)	27.2 (3.9)	<0.001
Weight change since baseline, kg, mean (SD)	−2.2 (5.4)	−2.7 (5.3)	−2.1 (5.4)	0.04
Weight loss 5% or more, n (%)	947 (25.9)	120 (28.2)	827 (25.6)	0.25
BMD measurements, mean (SD)				
Total hip				
Initial BMD, g/cm^2	0.97 (0.14)	0.90 (0.13)	0.97 (0.14)	<0.001
Initial BMD T-score	0.19 (1.12)	−0.36 (1.09)	0.26 (1.11)	<0.001
Annualized BMD percent change	−0.38 (0.75)	−0.52 (0.84)	−0.36 (0.74)	<0.001
Annualized BMD absolute change	−0.004 (0.007)	−0.005 (0.007)	−0.003 (0.007)	<0.001
Femoral neck				
Initial BMD, g/cm^2	0.79 (0.13)	0.73 (0.12)	0.80 (0.12)	<0.001
Initial BMD T-score	−0.57 (1.05)	−1.06 (0.98)	−0.51 (1.04)	<0.001
Annualized BMD percent change	−0.38 (0.90)	−0.52 (1.00)	−0.36 (0.89)	0.002
Annualized BMD absolute change	−0.003 (0.007)	−0.004 (0.007)	−0.003 (0.007)	0.007
Initial BMD T-score ≤ −1.5 at either site, n (%)	683 (18.7)	151 (35.4)	532 (16.5)	<0.001

Abbreviations: BMD, bone mineral density; PASE, Physical Activity Scale for the Elderly.
*Characteristics measured at repeat BMD measurement except if otherwise indicated that assessment was at initial BMD measurement.
†Multimorbid conditions include congestive heart failure, stroke, coronary heart disease, diabetes mellitus, chronic obstructive pulmonary disease/asthma, non-skin cancer, liver disease, renal disease, dementia, depression, Parkinsonism, and rheumatoid arthritis.

Mean value of initial hip BMD was lower and annualized rates of hip bone loss were slightly greater among men with vs those without an incident MOF. On average, men who experienced a MOF lost 0.52% or 0.005 g/cm^2 per year at the total hip compared with 0.36% or 0.003 g/cm^2 per year in men without MOF (*P* value < 0.001 for both comparisons).

In unadjusted and adjusted models based on initial total hip BMD, each SD decrement in initial BMD was associated with an increased risk of fracture during the follow-up period after the repeat BMD measurement (multivariable HR [95% CI] 1.77 [1.57-1.98] for MOF, 1.51 [1.39-1.64] for any clinical fracture, and 2.01 [1.69-2.38] for hip fracture) (Table 2). In similar models based on annualized percent total hip BMD change, each SD decrement in BMD change was also associated with risk of fracture (multivariable HR [95% CI] 1.22 [1.10-1.35] for MOF, 1.21 [1.12-1.31] for any clinical fracture, and 1.53 [1.33-1.75] for hip fracture). In models based on the combination of initial BMD and BMD change, both initial BMD and BMD change were associated with fracture risk independent of each other; but the association was stronger for initial BMD (multivariable HR [95% CI] per 1 SD decrement for initial BMD vs. BMD change 1.76 [1.57-1.98] vs. 1.19 [1.08-1.32] for MOF, 1.51 [1.39-1.64] vs. 1.20 [1.11-1.29] for any clinical fracture and 1.99 [1.67-2.36] vs.1.46 [1.28-1.67] for hip fracture).

Substitution of annualized absolute change for annualized percent change in total hip BMD and use of BMD at the femoral neck (Table 3) rather than at the total hip did not substantially alter these findings. Results were also similar in analyses excluding the 336 men taking osteoporosis drug treatment at the repeat BMD measurement or during follow-up (results not shown). In analyses that estimated associations of total hip BMD measures with risk of fracture outcomes using subdistribution hazards models accounting for death as a competing risk, findings were generally similar to analyses estimating associations using Cox proportional hazards models. However, for models based on the combination of initial BMD and BMD change that considered death as a competing risk (Table 4), multivariable associations of BMD change with fracture outcomes were further attenuated and not significant in the case of MOF.

Associations between annualized percent change in total hip BMD and risks of MOF and hip fracture (but not any clinical fracture) appeared to be somewhat more pronounced among men with higher baseline BMD T-score (ie, T-score at femoral neck or total hip > −1.5) (Table 5). For prediction of MOF, the HR (95% CI) per 1 SD decrement in percent BMD change was 1.41 (1.26-1.57) among men with initial T-score > −1.5 vs 1.12 (0.93-1.36) in men with initial T-score ≤ −1.5 (*P* value for interaction 0.009). For prediction of hip fracture, the HR (95% CI) per 1 SD decrement in percent BMD change was

Table 2. Associations between BMD measures and risk of fracture outcomes in models based on (1) initial total hip BMD, (2) annualized percent total hip BMD change, and (3) combination of initial total hip BMD and annualized percent total hip BMD change

Model	Hazard ratio (95% CI)*		
	Major osteoporotic fracture (N = 426)	Any clinical fracture (N = 793)	Hip fracture (N = 193)
Unadjusted model			
1. Initial BMD	1.90 (1.71-2.12)	1.59 (1.47-1.71)	2.13 (1.82-2.50)
2. BMD change	1.44 (1.31-1.57)	1.34 (1.25-1.43)	1.82 (1.63-2.03)
3. Initial BMD	1.88 (1.69-2.10)	1.58 (1.46-1.70)	2.09 (1.77-2.45)
+ BMD change	1.38 (1.27-1.51)	1.30 (1.22-1.39)	1.72 (1.54-1.91)
Base model†			
1. Initial BMD	1.77 (1.59-1.97)	1.52 (1.41-1.64)	1.98 (1.69-2.32)
2. BMD change	1.31 (1.19-1.44)	1.26 (1.17-1.35)	1.68 (1.49-1.90)
3. Initial BMD	1.77 (1.59-1.97)	1.52 (1.40-1.64)	1.96 (1.67-2.31)
+ BMD change	1.27 (1.16-1.40)	1.24 (1.15-1.33)	1.61 (1.43-1.81)
Multivariable model‡			
1. Initial BMD	1.77 (1.57-1.98)	1.51 (1.39-1.64)	2.01 (1.69-2.38)
2. BMD change	1.22 (1.10-1.35)	1.21 (1.12-1.31)	1.53 (1.33-1.75)
3. Initial BMD	1.76 (1.57-1.98)	1.51 (1.39-1.64)	1.99 (1.67-2.36)
+ BMD change	1.19 (1.08-1.32)	1.20 (1.11-1.29)	1.46 (1.28-1.67)

Abbreviations: BMD, bone mineral density; CI, confidence interval.
*Hazard ratio per 1 SD decrease in BMD measure.
†Adjusted for age, race, and study enrollment site.
‡Adjusted for age, race, study enrollment site, prior fracture, fall in past year, multimorbidity, physical activity, body mass index, and weight change.

Table 3. Associations between BMD measures and risk of fracture outcomes in models based on (1) initial femoral neck BMD, (2) annualized percent femoral neck BMD change, and (3) combination of initial femoral neck BMD and annualized percent femoral neck BMD change

Model	Hazard ratio (95% CI)*		
	Major osteoporotic fracture (N = 426)	Any clinical fracture (N = 793)	Hip fracture (N = 193)
Unadjusted model			
1. Initial BMD	1.88 (1.68-2.10)	1.62 (1.49-1.75)	2.24 (1.89-2.65)
2. BMD change	1.34 (1.21-1.47)	1.20 (1.12-1.29)	1.77 (1.56-2.01)
3. Initial BMD	1.90 (1.70-2.13)	1.63 (1.51-1.77)	2.24 (1.90-2.66)
+ BMD change	1.35 (1.22-1.48)	1.22 (1.13-1.31)	1.75 (1.54-1.97)
Base model†			
1. Initial BMD	1.74 (1.56-1.95)	1.54 (1.42-1.67)	2.05 (1.73-2.44)
2. BMD change	1.27 (1.15-1.40)	1.16 (1.08-1.25)	1.69 (1.48-1.93)
3. Initial BMD	1.77 (1.58-1.98)	1.55 (1.43-1.68)	2.08 (1.75-2.46)
+ BMD change	1.28 (1.17-1.41)	1.18 (1.09-1.27)	1.68 (1.48-1.90)
Multivariable model‡			
1. Initial BMD	1.72 (1.52-1.93)	1.53 (1.41-1.66)	2.06 (1.72-2.46)
2. BMD change	1.20 (1.08-1.32)	1.12 (1.04-1.21)	1.53 (1.33-1.76)
3. Initial BMD	1.73 (1.54-1.95)	1.54 (1.42-1.68)	2.07 (1.73-2.47)
+ BMD change	1.22 (1.10-1.34)	1.14 (1.06-1.23)	1.53 (1.33-1.76)

Abbreviations: BMD, bone mineral density.
*Hazard ratio per 1 SD decrease in BMD measure.
†Adjusted for age, race, and study enrollment site.
‡Adjusted for age, race, study enrollment site, prior fracture, fall in past year, multimorbidity, physical activity, body mass index and weight change.

1.82 (1.58-2.10) among men with initial T-score > –1.5 vs 1.49 (1.18-1.88) in men with initial T-score ≤ –1.5 (P value for interaction 0.006). Results were similar in analyses substituting annualized absolute for annualized percent total hip BMD change, though tests for interaction were of borderline significance (P value for interaction 0.05 for MOF and 0.09 for hip fracture). Findings were also essentially unchanged in analyses expressing initial BMD as ≤ median value at total

Table 4. Subdistribution models based on combination of initial total hip BMD and annualized percent total hip BMD change

Model	Hazard ratio (95% CI)*		
	Major osteoporotic fracture (N = 426)	Any clinical fracture (N = 793)	Hip fracture (N = 193)
Unadjusted model			
Initial BMD	1.78 (1.59-1.99)	1.51 (1.40-1.64)	1.93 (1.64-2.28)
+ BMD change	1.15 (1.06-1.25)	1.11 (1.04-1.18)	1.37 (1.23-1.53)
Base model†			
Initial BMD	1.72 (1.54-1.94)	1.49 (1.37-1.62)	1.90 (1.60-2.26)
+ BMD change	1.11 (1.02-1.22)	1.10 (1.03-1.18)	1.34 (1.19-1.50)
Multivariable model‡			
Initial BMD	1.71 (1.51-1.93)	1.48 (1.36-1.61)	1.94 (1.62-2.32)
+ BMD change	1.09 (0.99-1.20)	1.10 (1.02-1.19)	1.30 (1.13-1.48)

Abbreviations: BMD, bone mineral density.
*Hazard ratio per 1 SD decrease in BMD measure.
†Adjusted for age, race, and study enrollment site.
‡Adjusted for age, race, study enrollment site, prior fracture, fall in past year, multimorbidity, physical activity, body mass index and weight change.

Table 5. Association between annualized percent total hip BMD change and fracture outcomes within risk subgroups

Risk subgroup	Major osteoporotic fracture		Any clinical fracture		Hip fracture	
	HR (95% CI)*	*P* value for interaction	HR (95% CI)*	*P* value for interaction	HR (95% CI)*	*P* value for interaction
Age group						
≥80 years	1.34 (1.17-1.52)	0.71	1.34 (1.21-1.49)	0.14	1.65 (1.39-1.96)	0.39
<80 years	1.27 (1.10-1.45)		1.16 (1.05-1.29)		1.73 (1.47-2.04)	
Initial BMD T-score†						
≤ −1.5	1.12 (0.93-1.36)	0.009	1.18 (1.01-1.37)	0.12	1.49 (1.18-1.88)	0.006
> −1.5	1.41 (1.26-1.57)		1.28 (1.18-1.39)		1.82 (1.58-2.10)	
Weight loss 5% or more‡						
Yes	1.40 (1.17-1.68)	0.46	1.40 (1.22-1.61)	0.12	1.85 (1.50-2.27)	0.93
No	1.19 (1.07-1.34)		1.17 (1.07-1.27)		1.49 (1.26-1.76)	

Abbreviations: BMD, bone mineral density; HR, hazard ratio.
*Hazard ratio per 1 SD decrease in BMD change; adjusted for age, race, and enrollment site.
†T-score at the total hip or femoral neck.
‡Weight loss between initial and repeat BMD measurement.

hip vs > median value (*P* value for interaction between percent BMD change and initial BMD category 0.05 for MOF and 0.03 for hip fracture). In contrast, we found no evidence that the association of total hip BMD change and risk of any of the fracture outcomes differed by age group (≥80 years vs <80 years) or whether men had or had not experienced weight loss of 5% or more between initial and repeat BMD measurement.

In terms of discriminating between men who did vs those who did not experience a MOF during the follow-up period after the Y7 repeat BMD measurement, performance of models based on initial total hip BMD alone was somewhat better than that of models based on total hip BMD change alone and similar to that of models based on the combination of initial total hip BMD and total hip BMD change. The AUC (95% CI) for multivariable models was 0.68 (0.66-0.71) for the initial BMD model, 0.63 (0.61-0.66) for the BMD change model, and 0.69 (0.66-0.71) for the model based on combination of initial BMD and BMD change (Fig. 2A). With respect to the outcome of any clinical fracture, findings regarding the comparison of model discrimination were similar, though AUC values were slightly lower (AUC [95% CI] for multivariable models 0.64 [0.62-0.66] for the initial BMD model, 0.60 [0.58-0.62] for the BMD change model, and 0.64 [0.62-0.67] for the model based on combination of initial BMD and BMD change) (Fig. 2B). AUC values were highest for models predicting hip fracture. Hip fracture discrimination of the initial BMD model was somewhat better than that of the BMD change model; the AUC (95% CI) for multivariable models was 0.73 (0.69-0.76) for the initial BMD model vs 0.68 (0.64-0.72) for the BMD change model, *P* value for difference 0.02 (Fig. 2C). Discrimination of the combination of initial BMD and BMD change model appeared slightly better than that of the initial BMD model, but the difference in AUC values was smaller in magnitude and not significant for multivariable models (AUC [95% CI] 0.73 [0.69-0.76] for initial BMD model vs 0.74 [0.71-0.77] for the model based on combination of initial BMD and BMD change, *P* value for difference 0.06).

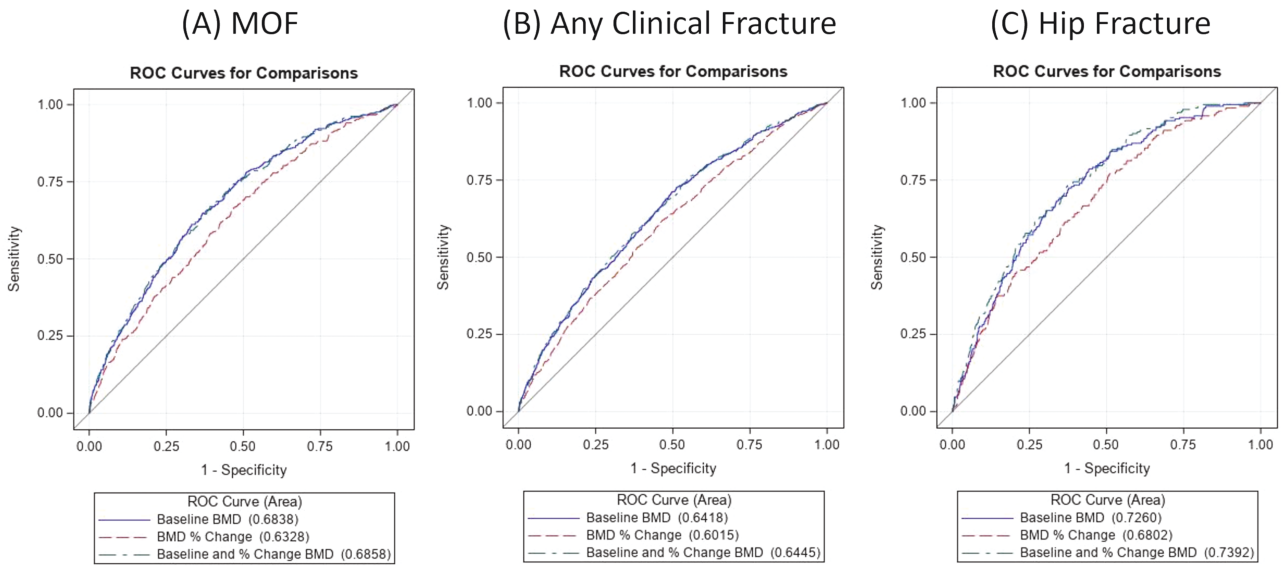

Figure 2. Receiver operating characteristic curves for models* predicting (A) major osteoporotic fracture (MOF), (B) any clinical fracture and (C) hip fracture. *Models based on initial total hip BMD, annualized percent total hip BMD change and the combination of initial total hip BMD and annualized percent total hip BMD change. All models are adjusted for age, race, study enrollment site, prior fracture, fall in past year, multimorbidity, physical activity, body mass index and weight change.

Results regarding the comparisons of model discrimination were generally similar in analyses stratified by characteristics including age group, category of initial BMD T-score, and weight loss category (Table 6).

Discussion

In this large population-based study of community-dwelling older men, repeating the hip BMD measurement 7 years after the initial BMD measurement did not meaningfully improve subsequent prediction of fracture including MOF, any clinical fracture and hip fracture. Performance of models based on initial BMD alone in discriminating between men with and without an incident fracture outcome was somewhat better than that of models based on BMD change alone and similar to that of models based on the combination of initial BMD and BMD change. While initial BMD (per 1 SD decrement) and BMD change (per 1 SD decrement) were associated with increased risk of fracture independent of each other, associations were stronger for initial BMD. These results suggest that there is little additional value in routinely incorporating a repeat BMD measurement 7 years after the initial BMD measurement into a screening strategy to assess fracture risk in older community-dwelling men.

Our findings are consistent with those of previous studies conducted in postmenopausal and older women that evaluated the value of repeat hip BMD screening in fracture prediction. A study in 4124 older women (7) (mean age 72 years at the initial BMD) found no significant differences between a model based on initial BMD, repeat BMD 8 years later, and a model based on the combination of initial BMD and BMD change in discriminating between women who did and did not experience fracture (any non-spine, hip fracture) during an average follow-up of 5 years after the repeat BMD. Of note, the AUC statistic of the hip fracture models based on initial total hip BMD (0.73) and the combination of initial total hip BMD and BMD change at the total hip (0.74) were identical to those observed in our study of older community-dwelling men. Similarly, a study of 7219 postmenopausal women (8) (mean age 66 years at repeat BMD) with repeat total hip BMD 3 years after the initial BMD reported that discrimination of MOF and hip fracture during the 9 years after the repeat BMD was essentially indistinguishable using models based on initial BMD (AUC 0.61 for MOF and 0.71 for hip fracture) compared with models based on the combination of initial BMD and BMD change (AUC 0.61 for MOF and 0.73 for hip fracture). Furthermore, investigations in middle-aged (22), postmenopausal (8), and older women (23) also found that initial BMD (expressed as a continuous measure) remained a strong robust predictor of fracture risk after adjustment for BMD change (expressed as a continuous measure), while BMD change was weakly or not associated with fracture risk after consideration of initial BMD. Of note, the modest associations of BMD change with risk of fracture after adjustment for initial BMD that we observed in our study of older men were further attenuated in analyses that accounted for the competing risk of mortality. The ability of baseline hip BMD to predict subsequent risk of hip and nonvertebral fractures over 20 to 25 years of follow-up was previously investigated in a cohort of 8130 community-dwelling women aged 67 years and older (mean age 73.4 years) (24). This study reported that initial hip BMD was a robust predictor of long-term risk of fracture with little or no degradation over time.

Fewer studies examining repeat BMD screening and fracture prediction have included or been limited to men. Findings from our large study of 3651 men are in agreement with those of a previous study conducted in 802 older adults (mean age 75 years) including 310 men (9). In this study, a repeat femoral neck BMD 4 years after the initial BMD did not meaningfully improve discrimination of incident MOF and hip fracture during an average follow-up of 9.6 years after the repeat BMD. For example, the AUC statistic for hip fracture was 0.71 for the initial BMD model, 0.68 for the BMD

Table 6. Comparison of AUC statistics in fracture outcome models based on initial total hip BMD, annualized percent total hip BMD change, and combination of initial total hip BMD and annualized percent total hip BMD change

	Initial BMD	BMD change	Initial BMD + BMD change
Major osteoporotic fracture			
Overall	0.67 (0.65-0.70)	0.61 (0.58-0.64)	0.68 (0.65-0.70)
Age			
≥80 years	0.67 (0.63-0.71)	0.58 (0.54-0.62)	0.68 (0.64-0.71)
<80 years	0.67 (0.63-0.70)	0.60 (0.56-0.64)	0.67 (0.63-0.71)
Baseline BMD T-score†			
≤ −1.5	0.62 (0.57-0.67)	0.58 (0.53-0.63)	0.62 (0.57-0.67)
> −1.5	0.64 (0.61-0.67)	0.62 (0.58-0.65)	0.65 (0.62-0.68)
Weight loss 5% or more‡			
Yes	0.68 (0.63-0.74)	0.60 (0.55-0.65)	0.69 (0.64-0.74)
No	0.67 (0.64-0.70)	0.62 (0.59-0.65)	0.67(0.64-0.71)
Any clinical fracture			
Overall	0.63 (0.61-0.66)	0.58 (0.56-0.60)	0.64 (0.62-0.66)
Age			
≥80 years	0.64 (0.61-0.67)	0.57(0.54-0.61)	0.64(0.61-0.68)
<80 years	0.63 (0.61-0.66)	0.58 (0.55-0.61)	0.63(0.61-0.66)
Baseline BMD T-score†			
≤ −1.5	0.62 (0.58-0.67)	0.59 (0.55-0.64)	0.62 (0.58-0.67)
> −1.5	0.61 (0.58-0.63)	0.58 (0.55-0.60)	0.61 (0.58-0.63)
Weight loss 5% or more‡			
Yes	0.67 (0.63-0.71)	0.62 (0.58-0.67)	0.67 (0.63-0.72)
No	0.62 (0.60-0.65)	0.58 (0.55-0.60)	0.63 (0.60-0.65)
Hip fracture			
Overall	0.70 (0.66-0.74)	0.66 (0.63-0.70)	0.73 (0.69-0.76)
Age			
≥80 years	0.68 (0.63-0.73)	0.63 (0.58-0.69)	0.70 (0.65-0.74)
<80 years	0.71 (0.65-0.76)	0.67 (0.61-0.72)	0.74 (0.69-0.79)
Baseline BMD T-score†			
≤ −1.5	0.62 (0.55-0.69)	0.61 (0.55-0.68)	0.63 (0.57-0.70)
> −1.5	0.67 (0.62-0.72)	0.69 (0.65-0.74)	0.72 (0.67-0.76)
Weight loss 5% or more‡			
Yes	0.68 (0.62-0.75)	0.68 (0.62-0.74)	0.72 (0.66-0.78)
No	0.72 (0.68-0.76)	0.67 (0.62-0.72)	0.74 (0.70-0.78)

Abbreviations: AUC, area under the curve; BMD, bone mineral density.
*Adjusted for age, race, and enrollment site.
†T-score at the total hip or femoral neck.
‡Weight loss between initial and repeat BMD measurement.

change model, and 0.72 for the model based on the combination of initial BMD and BMD change. Models performed similarly in analyses stratified by sex. A Canadian study of 5502 middle-aged and older adults that included 1417 men (mean age 64 years) (25) reported that a model based on BMD change (expressed as a continuous variable) was not better than a model based on initial BMD (expressed as a continuous variable and measured within the first 5 years of the study) in predicting the odds of most self-reported fracture outcomes in men during the first 7 years of the study including main (hip, pelvis, vertebral, rib, and forearm), forearm, and rib fractures. However, the model based on total hip BMD change (but not femoral neck BMD change) was better than the model based on initial BMD in predicting any low-trauma fracture in men. Unlike our investigation, this study analyzed fracture outcomes during a time period that was concurrent with the time period of measurement of BMD change and did not address whether repeating BMD improved the prediction of subsequent fracture risk. Of importance, a prior study in our MrOS cohort (10) estimated BMD change using hip BMD measurements at 2 to 3 time points over 4.6 years with random effects linear regression models that included a quadratic term for age to account for nonlinear increases in BMD loss with advancing age. After adjustment for initial BMD, men with accelerated BMD loss (estimated BMD change ≥ 1 SD below mean BMD change) compared with men who maintained BMD (estimated BMD change ≥ 0 g/cm^2) had a 7-fold increase in risk of hip fracture and a 2-fold increase in risk of any nonvertebral fracture during an average follow-up of 4.5 years after the final BMD. There was no difference in fracture risk between men with expected BMD loss (estimated BMD change between 0 and

1 SD below mean BMD change) and those who maintained BMD. The statistical approach used to estimate BMD change differed between the previous and present study. Our current study addressed the clinical utility of routinely integrating repeat BMD testing into a screening strategy to assess subsequent fracture risk in older men. Thus, we analyzed simple linear BMD change rather than rate of BMD change generated from mixed effects models, as the former (but not the latter) measure is readily available in the practice setting for shared clinical decision making such as whether or not to recommend initiation of drug treatment for fracture prevention. In addition, the previous analysis did not address the extent to which the repeated BMD measurements improved fracture risk prediction.

Our findings did not vary by clinical characteristics, including age group or weight change category. However, we found some evidence to suggest that the association of BMD change (expressed as annualized percent or absolute change) with risks of MOF and hip fracture (but not any clinical fracture) was slightly higher in magnitude among men with higher vs lower initial BMD T-score. This unexpected finding may in part be due to the phenomenon of regression to the mean, although it was present in analyses stratified by the median value of initial BMD as well as in analyses stratified at an initial T-score of –1.5. While previous studies (7, 9) have not reported evidence of interactions between initial BMD and BMD change for the prediction of fracture risk, a prior investigation in 4498 women aged 40 years and older (22) found that higher baseline BMD was the factor most strongly associated with a subsequent decrease in BMD.

Our results have implications for screening strategies to assess fracture risk in older men. Several organizations (4-6) have endorsed osteoporosis screening with initial BMD testing in older men but have not addressed the timing of re-screening with repeat BMD measurement. In our population-based cohort of older relatively healthy, community-dwelling men who would be candidates for osteoporosis screening, repeat BMD testing 7 years after the initial BMD measurement provided little additional value beyond the initial BMD in predicting risk of future fracture. Our results confirm and extend those of a previous analysis of our cohort (26) that examined the utility of repeat BMD testing in identifying older men who transition to osteoporosis (BMD T-score ≤ –2.5). In the previous study, only 0.2% of the men with initial BMD T-score > –1.5 (78% of the cohort) developed osteoporosis during an average follow-up of 8.7 years and among men with initial BMD T-score between –1.50 and –2.00 (19% of the cohort), the estimated time for 10% to transition to osteoporosis was 8.5 years.

Strengths of our study include the large cohort of well-characterized community-dwelling men, rigorous quality control of hip BMD measurements performed 7 years apart, nearly complete long-term follow-up of participants for vital status and fractures, and confirmation of incident fractures with radiographic reports. However, there are some limitations. Among our cohort of relatively healthy older men, the prevalence of osteoporosis was low at baseline, in agreement with that reported in community-dwelling men 65 years and older enrolled in the nationally representative National Health and Nutrition Examination Survey 2005-2010 (27). Very few men without osteoporosis at baseline transitioned to osteoporosis 7 years later at the repeat BMD measurement. Thus, our findings are relevant to a screening population of older men. They do not apply to older men with intervening conditions that markedly increase risk for accelerated bone loss or to individuals with secondary causes of osteoporosis for whom repeat BMD testing may be indicated. Our study population included predominantly White men and results may not be generalizable to older men of other racial/ethnic groups. Our investigation addressed the value of incorporating a repeat BMD measurement into a screening strategy to assess fracture risk in older men but did not evaluate the utility of BMD measurements in monitoring response to osteoporosis drug treatment in this population.

In conclusion, a repeat BMD measurement 7 years after the initial BMD measurement did not result in a meaningful improvement in subsequent fracture prediction at the population level in community-dwelling older men. These findings suggest that repeat BMD testing within this time interval should not be routinely incorporated into screening strategies to evaluate fracture risk in this population. Future research is needed to inform recommended BMD testing intervals in targeted subgroups of older men at high risk of transitioning to osteoporosis, accelerated bone loss or high fracture risk.

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Data Availability

MrOS data is available to the public via the "MrOS Online" website (https://mrosonline.ucsf.edu/).

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