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Bone Density Screening and Re-screening in Postmenopausal Women and Older Men

Margaret L. Gourlay[1], **Robert A. Overman**[2], and **Kristine E. Ensrud**[3,4]

Margaret L. Gourlay: margaret_gourlay@med.unc.edu; Robert A. Overman: overmar@unc.edu; Kristine E. Ensrud: ensru001@umn.edu

[1]Department of Family Medicine, University of North Carolina, Aycock Building; Manning Drive, CB #7595, Chapel Hill, NC 27599-7595, USA

[2]Division of Pharmaceutical Outcomes and Policy, UNC Eshelman School of Pharmacy, University of North Carolina, Kerr Hall, Room 2304, North Carolina, Chapel Hill, NC 27599-7573, USA

[3]Department of Medicine and Division of Epidemiology, General Internal Medicine (111-0), University of Minnesota, Minneapolis, MN 55417, USA

[4]Department of Medicine, VA Medical Center, One Veterans Drive, Minneapolis, MN, USA

Abstract

Clinical practice guidelines universally recommend bone mineral density (BMD) screening to identify osteoporosis in women aged 65 years and older. Risk assessment is recommended to guide BMD screening in postmenopausal women under age 65. Insufficient data are available to inform standard ages to start and stop BMD screening in postmenopausal women. Based on longitudinal studies of incident osteoporosis and fracture in postmenopausal women, an initial BMD test should be ordered for all women aged 65, and the frequency of re-screening should be based on age and BMD *T* score (more frequent testing for older age and lower *T* score). Although clinical practice guidelines recommend BMD screening according to risk factors for fracture in postmenopausal women under age 65, no standard approach to risk assessment exists. Minimal evidence is available to guide osteoporosis screening in men, but some experts recommend initiation of BMD screening in men at age 70.

Keywords

Bone density; Men; Osteoporosis; Postmenopausal women; Screening

Correspondence to: Margaret L. Gourlay, margaret_gourlay@med.unc.edu.

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent This article contains no studies with human or animal subjects performed by the author.

Introduction

The past decade (2005–2015) has been an active period of progress in research on osteoporosis screening. This article reviews epidemiological issues in screening and highlights recent data on the use of bone mineral density (BMD) screening to identify osteoporosis in postmenopausal women and older men.

Key Components of the BMD Screening Program

The purpose of BMD screening is to identify a pre-symptomatic condition (osteoporosis) that can be treated to avoid morbidity and mortality from osteoporotic fractures [1]. The key components of a BMD screening program are as follows:

The Screened Population: Well Individuals

To meet the epidemiological criteria for a screened population, individuals who undergo BMD screening must be asymptomatic and without a history of fragility fracture (e.g., hip or clinical vertebral fracture), not taking pharmacologic treatment to prevent fractures, and without an identified secondary cause of osteoporosis [2].

Clinical Outcome: Major Osteoporotic Fracture

Fractures cause pain, immobility or impaired mobility, lost work days, and decreased quality of life and are associated with increased outpatient and inpatient costs that are especially high for hip fractures [3]. While both low-trauma and high-trauma fractures might be reduced by pharmacologic treatment in individuals with osteoporosis by BMD criteria or existing vertebral fracture [4], clinical trials have focused on agents to reduce “osteoporotic fractures” or “fragility fractures” associated with minimal trauma. No consensus exists regarding the specific fracture sites that should be considered “osteoporotic” or classified as fragility-related [5, 6]. Also, although lower BMD predicts fracture risk [7], most fractures in older adults occur in individuals who do not have osteoporosis by BMD criteria [8, 9]. In this article, we focus on the clinical outcome of “major osteoporotic fracture,” defined by the World Health Organization (WHO) to include clinical vertebral fractures and fractures at the hip, proximal humerus, or wrist [10]. Of these, hip and clinical vertebral fractures are the most clinically relevant fracture outcomes because of their associated high morbidity and mortality [11].

Target Condition of Screening: Osteoporosis by BMD Criteria

To define an appropriate target condition for BMD screening, the WHO developed diagnostic criteria for osteoporosis in 1994 based on the BMD *T* score (standard deviation from young normative BMD mean) at the lumbar spine and two sites at the hip (femoral neck and total hip) measured by dual energy x-ray absorptiometry (DXA) [12]. Osteoporosis was defined as a *T* score ≤−2.50 at any of the three sites, osteopenia as lowest *T* score between −2.50 and −1.00 (not inclusive) at any site, and normal BMD as *T* score ≥−1.00 at all sites [12].

The WHO described the *T* score cut point for osteoporosis as follows [12]:

> "…all cut-off values are somewhat arbitrary, but a measured value of bone mineral more than 2.5 standard deviations below the mean for young healthy women at any site (spine, hip, mid-radius) identifies 30 % of all postmenopausal women as having osteoporosis, more than half of whom will have sustained a prior fracture of the proximal femur, spine, distal forearm, proximal humerus or pelvis."

Despite the arbitrary and secular nature of the cut point, the clinical relevance of the −2.5 *T* score was later substantiated by multiple rigorous randomized, placebo-controlled trials demonstrating that treatment of osteoporosis by WHO diagnostic criteria reduced risk of clinical vertebral fractures and hip fractures, with less convincing evidence of reduction of fractures at other sites [13–18]. The most important working aspects of the WHO diagnostic criteria are as follows:

1. The criteria apply to postmenopausal women and have been extrapolated to older men. Fracture risk cannot be accurately estimated by *T* scores measured in premenopausal women or young men, and those individuals are not candidates for screening and treatment within the general population.
2. While densitometer manufacturers include BMD norms for both women and men, the International Osteoporosis Foundation [19] and the International Society for Clinical Densitometry [20] recommend that a uniform Caucasian (non-race-adjusted) female reference database should be used to calculate *T* scores for men of all ethnic groups. Some experts prefer to calculate *T* scores based on male norms, which results in a higher proportion of the male population being diagnosed as osteoporotic [21].

Osteoporosis by BMD criteria is still the target condition for screening that is substantiated by the highest level of evidence [2]. The efficacy of pharmacologic treatment in patients selected on the basis of fracture risk scores calculated with or without BMD has not been tested in randomized controlled trials [22]. In 2014, the National Bone Health Alliance proposed an alternative definition of "osteoporosis" that included osteoporosis by BMD criteria as well as hip fracture and osteopenia-associated vertebral, proximal humerus, pelvis or some wrist fractures, or 10-year fracture risk estimations of ≥3 % for hip or 20 % for major osteoporotic fracture calculated using the FRAX fracture risk tool [23]. This alternative definition cannot be used in studies of screening because it combines the target condition for screening (osteoporosis by BMD criteria) with the clinical outcome that screening attempts to prevent (fracture). This leads to time-to-disease estimates that are not interpretable for the prevention of fracture. Other experts have recommended against expansion of the definition of osteoporosis unless further evidence-based research shows that the benefits of such an expansion outweigh the harms [24].

Intervention for Screen-Positive Patients: Pharmacologic Treatment to Prevent Fracture

The clinical efficacy of screening depends on treatment efficacy, i.e., a screening program can only be successful if available treatments effectively reduce clinically detectable disease. If effective treatments are not available, a test with 100 % accuracy is useless. For this reason, randomized controlled trials of treatment precede randomized trials of screening.

In 2002, BMD screening programs were given a Grade C evidence rating (evidence substantiates offering or providing this service for selected patients depending on individual circumstances) by the US Preventive Services Task Force after data from randomized controlled trials demonstrated fragility fracture reduction in individuals with osteoporosis by BMD criteria who received pharmacologic treatment [25]. While the WHO's −2.50 *T* score cut point was in some sense an arbitrary cutoff, it proved to be a clinically relevant threshold for primary fracture prevention in subsequent randomized controlled trials of pharmacologic treatment. To date, reduction in clinical fracture events has only been demonstrated in RCTs in postmenopausal women with osteoporosis by WHO diagnostic criteria or with existing radiographic vertebral fractures or history of clinical vertebral fractures or in patients with recent hip fracture regardless of their *T* score level [13–18].

Despite the lack of direct RCT evidence demonstrating that BMD screening reduces fractures or mortality, the USPSTF concluded in 2011 that the net benefit of osteoporosis screening was at least moderate in women aged 65 and older and in younger postmenopausal women with fracture risk at least as high as a 65-year-old white woman who has no additional risk factors (grade B evidence) [26]. This approach has not been tested prospectively and is problematic because of the low level of accuracy of the USPSTF risk assessment approach to identify younger postmenopausal women who later develop osteoporosis or major fracture [27, 28] (see "Postmenopausal Women/Age to Start Osteoporosis Screening").

Other Uses of BMD Testing

Osteoporosis screening is one of several uses of BMD testing. BMD testing may also be ordered to rule out osteoporosis in patients with secondary causes of BMD loss, for treatment monitoring or for surveillance after a major fragility fracture event. In the latter cases, patients who undergo BMD testing have a different risk of future fracture than the general population and thereby no longer qualify for a "screening" BMD test.

Postmenopausal Women

According to estimates from the National Health and Nutrition Examination Survey (NHANES) 2005–2008, the prevalence of osteoporosis at the femoral neck or lumbar spine ranges from 6.8 % in women aged 50 to 59 to 34.9 % in women aged 80 and older [29]. Among US women aged 65 and older, approximately 25.1 % have osteoporosis (BMD value at least 2.5 standard deviation units below the mean) and 52.3 % have low bone mass (BMD value between 1.0 and 2.5 standard deviation units below the mean) calculated using BMD norms for young non-Hispanic white females, age-adjusted to the 2010 Census Bureau estimates [30]. A meta-analysis of data from 12 cohort studies including 29,082 women reported that at the age of 65 years, women's risk ratio for hip fractures increased by 2.88 (95 % CI 2.31, 3.59) for each SD decrease in BMD, and their risk of osteoporotic fractures (including hip, humeral or limb fractures and fractures of the spine, pelvis, ribs, distal forearm and forearm, clavicle, scapula or sternum) increased by 1.38 (95 % CI, 1.28, 1.48) per SD decrease in BMD [31, 32].

Age to Start Osteoporosis Screening

No standard age for starting BMD screening is recommended in clinical practice guidelines. Epidemiological data suggest that mass osteoporosis screening and treatment in postmenopausal women under age 60 is likely to be very inefficient. For example, the USPSTF estimated the number needed to screen to prevent one hip fracture would be more than 4000 for women aged 50–59 due to low osteoporosis prevalence and low fracture risk before age 60 [33]. A 2008 Cochrane review estimated that the number needed to treat (NNT) for alendronate to prevent the first hip fracture was nonestimable in postmenopausal women aged 50–54 and 943 for women aged 55–59, and the NNT to prevent the first vertebral fracture was 1111 for aged 50–54 and 556 for aged 55–59 [34]. A review of the cost-effectiveness literature concluded that treatment with bisphosphonates is likely to be cost-effective in populations aged 70 and older, but that “the younger the cohorts and the fewer risk factors they have, the less cost-effective treatment with a bisphosphonate is” [35].

No data are available on the benefit of osteoporosis treatment beginning at age 50–59 and continuing over three or four decades. Because of rapid rates of BMD loss and trabecular perforation during the perimenopausal transition, some experts have proposed antiresorptive treatment during early menopause [36], However, the long-term benefit of early therapy may be limited because of drug washout after discontinuation. Hormone therapy used in the early postmenopausal period does not confer fracture protection after discontinuation [37]. Similarly, withdrawal of alendronate leads to BMD declines within 2 years [38, 39]. Potential harms from early therapy must also be considered. Because younger postmenopausal women have lower immediate risk of fragility fractures, they are substantially more likely than postmenopausal women aged 60 and older to sustain harms that outweigh benefits from early treatment. Harms of screening include knowledge of low bone density that causes anxiety despite lack of symptoms [40]. Early treatment may lead to prolonged bisphosphonate use, which has been associated with osteonecrosis of the jaw [41, 42] and atypical femoral fractures [43, 44]. Finally, overtreating younger postmenopausal women when their fracture risk is low may leave them with few or no treatment options in their early 70s, when hip fractures start to increase exponentially [45]. This could potentially decrease the lifetime potential for net treatment benefit.

In the absence of definitive data on the optimal age to start BMD screening, clinical practice guidelines recommend consideration of BMD testing in postmenopausal women as young as 50 years, with risk factor assessment to guide the decision to order testing from age 50 to 64 [46, 47]. In its 2010 systematic review on osteoporosis screening, the USPSTF assessed studies of 21 externally validated clinical risk-assessment tools including 1 to more than 15 variables [48]. Most of the tools included age, weight or body mass index, and previous fracture. Risk tools to predict low BMD (area under the curve [AUC], 0.13 to 0.87) and fractures (AUC, 0.48 to 0.89) were evaluated; simple and complex instruments performed similarly. No tool demonstrated high AUC estimates in several studies. “Important methodological limitations of studies include nonrepresentative samples, cross-sectional rather than prospective data collection, inconsistent performance of the reference standard, and differences in performance measures across studies” [48]. A 2014 diagnostic accuracy analysis found that the Osteoporosis Self-assessment Tool (OST) and the Simple Calculated

Osteoporosis Risk Estimate (SCORE) risk assessment tool had fair to poor diagnostic accuracy and that the US Preventive Services Task Force risk assessment strategy based on a fracture risk score had poor diagnostic accuracy to identify postmenopausal women aged 50 to 64 with incident osteoporosis by BMD criteria or major osteoporotic fracture over the subsequent 10 years [27, 28]. While the principle behind risk assessment to decide a screening test has face validity, a two-step process of risk assessment followed by BMD screening decision has not been tested prospectively, and there is no consensus regarding which risk factors or which risk tools to use for selection of candidates for BMD screening [49].

In a study of osteoporosis incidence in postmenopausal women aged 50 to 64 at baseline participating in the Women's Health Initiative [50], tabulations of fracture events (Table 1) during study follow-up suggested that the lowest *T* scores within the osteopenia range (*T* score −2.49 to −2.00) were relatively infrequent but occurred across all age ranges of younger postmenopausal women. Development of osteoporosis by BMD criteria over 11 years of follow-up was rare in those who had baseline *T* scores >−1.50. The longitudinal results for this study (Fig. 1) also indicated that younger postmenopausal women with baseline *T* scores −2.49 to −2.00 transitioned to osteoporosis as rapidly as women aged 67 and older. These findings suggest that DXA testing has a role for some postmenopausal women across the age range of 50 to 64. However, evidence is lacking to inform a standard approach to selection of the best candidates for BMD screening and optimal timing of treatment in this age range.

A 2015 analysis documented a decrease in the BMD testing rate in commercially insured postmenopausal women aged 50 to 64 between 2006 and 2012, during a time period when Medicare reimbursement for DXA BMD testing declined significantly [51]. An estimated 667,982 DXA scans were performed for younger postmenopausal women in 2012, compared to an estimated 2,338,240 DXA tests performed in physician offices and hospitals for Medicare beneficiaries in 2009 [51, 52].

Osteoporosis Screening Intervals

Decisions regarding bone density screening intervals were initially based on machine precision specifications, i.e., the magnitude of the change in BMD that indicates real biological change, called the least significant change (LSC) [53]. A 2007 prospective observational study suggested that a second DXA BMD test up to 8 years after the first provided little additional fracture prediction in women aged 65 years and older [54]. A 2009 population-based study including 1008 women and 750 men aged 60 years and older at baseline estimated the time to development of osteoporosis or incident fragility fracture [55]. This study contributed important information regarding fracture risk stratification according to age and BMD *T* score; however, results were difficult to interpret with respect to osteoporosis screening because the pre-symptomatic condition of osteoporosis was combined with fragility fractures in the outcome measure.

A 2012 longitudinal study of 4957 women aged 67 and older at baseline tested a BMD screening interval defined as the estimated time for 10 % of women to transition from

normal BMD or osteopenia to osteoporosis. Important aspects of the study with respect to clinical implementation included its large size, 15 years of concurrent imaging and fracture follow-up, and methodology that treated pharmacologic treatment and incident hip and spine fracture as competing risks rather than censoring criteria. The same authors documented time-to-fracture estimates according to baseline age groups of postmenopausal women aged 50 to 64 in an effort to separate age groups at lower and higher risk of major osteoporotic fracture [50].

A comparison of the cumulative incidence of osteoporosis in women aged 67 and older participating in the Study of Osteoporotic Fractures (SOF) vs. women aged 50 to 64 participating in the Women's Health Initiative (WHI) from the latter two analyses is shown in Fig. 1 [50, 56••]. Figure 1 demonstrates that postmenopausal women aged 50 and older with baseline *T* scores between −2.49 and −2.00 may have a rapid transition to osteoporosis. Conversely, postmenopausal women with baseline *T* scores >−1.50 transition to osteoporosis much more slowly. For postmenopausal women aged 50 to 64 who undergo BMD testing and have baseline *T* scores >−1.50, the transition to osteoporosis is so slow that clinicians might consider deferring the next DXA test to age 65, the age at which routine BMD screening is recommended for all women.

While time-to-osteoporosis estimates are helpful, the timing of screening intervals is still a subjective decision in primary care practice. Results from the cited studies are only relevant for the screened population of well individuals, not patients with pre-existing fracture, treatment, or secondary causes of osteoporosis. The plots in Fig. 1 use a 10 % incidence threshold as the metric, i.e., the estimated time for 10 % of the *T* score group or age group to develop osteoporosis. A lower or higher threshold might be considered according to the patient's baseline risk factors for fracture or because of the patient's past history.

Age to Stop Osteoporosis Screening

An age to stop or decrease use of BMD testing has not been examined, and policy statements do not recommend cessation of screening at a specific age. In women aged 70 to 80 years at baseline, osteoporosis treatment is effective and mass BMD screening has been assessed as more cost-effective than no screening or screening only in women with at least one risk factor for fracture [13, 57–60]. Women aged 80 and older are less well studied because they are represented in smaller numbers in cohort studies of BMD and fracture. With increasing age, the rate of non-fracture death greatly outweighs fracture-related deaths, making BMD screening less likely to be beneficial.

Older Men

According to estimates from the NHANES 2005–2008 [29], the prevalence of osteoporosis at the femoral neck or lumbar spine ranges from 3.4 % in men aged 50 to 59 to 10.9 % in men aged 80 and older [29]. Among US men aged 65 and older, approximately 5.7 % have osteoporosis (BMD value at least 2.5 standard deviation units below the mean) and 44.2 % have low bone mass (BMD value between 1.0 and 2.5 standard deviation units below the mean) calculated using BMD norms for young non-Hispanic white females, age-adjusted to the 2010 Census Bureau estimates [30]. A meta-analysis of data from 12 cohort studies

including 9891 men reported that at the age of 65 years, men's risk ratio for hip fractures increased by 2.94 (95 % CI, 2.02, 4.27) for each SD decrease in BMD, and their risk of osteoporotic fractures (including hip, humeral or limb fractures and fractures of the spine, pelvis, ribs, distal forearm and forearm, clavicle, scapula or sternum) increased by 1.41 (95 % CI, 1.33, 1.51) per SD decrease in BMD [31, 32].

Osteoporosis and Fracture Risk in Men

A 1998 prospective study of a Dutch cohort of 7046 individuals (2778 men) aged 55 years and older suggested that the risk of hip fracture in men and women is similar at the same femoral neck absolute bone density level [61], but a 2006 analysis found that men aged 65 and older had a lower risk of fracture at every *T* score of hip BMD compared to same-aged women [62]. On average, men have higher BMD than age-matched women throughout life, and their rate of BMD loss in older age is slower than that for women [63]. As a result, fewer men develop osteoporosis, and fragility fractures occur less often in men than in women.

Despite lower overall fracture incidence, men have greater morbidity and mortality associated with hip fractures compared to women. Men are more likely than women to die within 1 year after a hip fracture [64]. Almost one third of men with hip fractures have subsequent fractures (of any type) during their remaining lifetime [65]. After a hip fracture, most new fractures occur in relatively younger men within 5 years, whereas most aged 75 and older die before experiencing a new fracture [65]. Fractures at typical osteoporotic sites are associated with increased mortality across all age groups of women and men, particularly in men [66–71].

Evidence for Pharmacologic Treatment Efficacy in Men

Treatment with oral bisphosphonates is effective in reducing risk of incident radiographic vertebral fractures in RCTs up to 3 years in length conducted in men aged 30s to 80s, about half of whom had existing radiographic vertebral fracture and many of whom had osteoporosis by BMD criteria at baseline [72–78]. A 2012 randomized controlled trial of older men with osteoporosis treated with zoledronic acid demonstrated significant reduction in the primary endpoint of radiographic vertebral fracture [79••]. However, no RCT has demonstrated prevention of clinical fractures in men with or without osteoporosis at baseline.

The optimal *T* score cut point for treatment is uncertain for older men, but data from Ensrud et al. suggest that older men with *T* scores ≤−2.50 calculated using BMD norms for young white women may be most likely to benefit from pharmacologic treatment to reduce fracture [80••].

Lack of a BMD Screening Protocol in Men

No standard BMD screening schedule exists for men, but several subspecialty organizations have offered recommendations based on expert opinion. Based on literature reviews by expert panels, the National Osteoporosis Foundation [46] and International Society for

Clinical Densitometry [81] supported BMD screening in all men aged 70 and older and in men aged 50 to 69 with clinical risk factors for fracture. The American College of Physicians recommended that osteoporosis risk factors be evaluated in men aged 50 to 69 to determine whether DXA testing should be considered [82, 83]. They listed important osteoporosis risk factors in men to be age (>70 years), low body weight (body mass index <20 to 25 kg/m^2), weight loss, physical inactivity, corticosteroid use, androgen deprivation therapy, and previous fragility fracture. Studies are needed to compare performance of strategies to identify older men who are candidates for osteoporosis screening.

Conclusions

The state of the art of BMD screening has been strengthened by new data published since 2005. Despite a number of studies of risk assessment tools to select postmenopausal women under age 65 for osteoporosis screening, no standard approach has been tested prospectively. The very low fracture risk in women aged 50 to 54 argues against frequent screening in this age range. Clinical guidelines universally recommend routine BMD screening in women aged 65 and older, and recent data suggest that women with baseline *T* scores ≤−1.50 can benefit from more frequent BMD screening than women with *T* scores >−1.50. Minimal evidence exists to inform BMD screening in older men, and studies are needed to compare the performance of potential strategies to select individuals for osteoporosis screening in this population.

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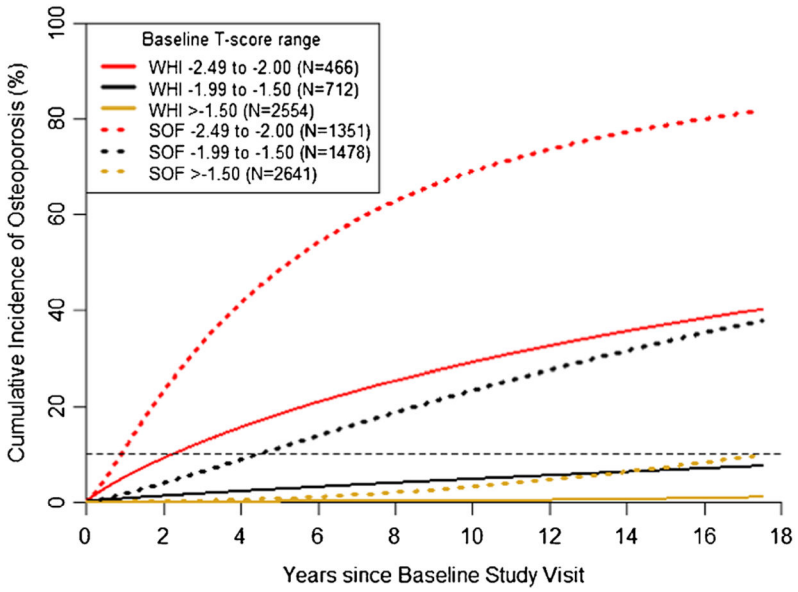

Fig. 1.

Cumulative incidence of osteoporosis in postmenopausal women aged 50 to 64 (Women's Health Initiative) vs. 67 years and older (Study of Osteoporotic Fractures). The intersection of each plot with the 10 % *dotted line* threshold is the time for 10 % of women to develop osteoporosis by BMD criteria

Table 1

Proportion of WHI participants aged 50 to 64 at baseline who developed osteoporosis after up to 11 years of BMD follow-up [50]

Baseline *T* score range/age[a]	Total *N*[b]	Developed osteoporosis, *N* (%)[a]
>−1.50	2554	2 (0.08)
age 50–54	798	1 (0.13)
age 55–59	896	0 (0.00)
age 60–64	860	1 (0.12)
−1.99 to −1.50	712	25 (3.51)
age 50–54	150	5 (3.33)
age 55–59	242	10 (4.13)
age 60–64	320	10 (3.13)
−2.49 to −2.00	466	101 (21.67)
age 50–54	83	24 (28.92)
age 55–59	149	30 (20.13)
age 60–64	234	47 (20.09)

[a] BMD *T* scores at the femoral neck, total hip, or lumbar spine calculated using BMD norms for young white women

[b] Tabulations account for the competing risks of incident antifracture treatment, hip, or clinical vertebral fracture or death