CLINICAL RESEARCH STUDY

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Osteoporosis in the Women's Health Initiative: Another Treatment Gap?

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ABSTRACT

BACKGROUND: Osteoporotic fractures are associated with high morbidity, mortality, and cost.

METHODS: We performed a post hoc analysis of the Women's Health Initiative (WHI) clinical trials data to assess osteoporosis treatment and identify participant characteristics associated with utilization of osteoporosis medication(s) after new diagnoses of osteoporosis or fracture. Information from visits prior to and immediately subsequent to the first fracture event or osteoporosis diagnosis were evaluated for medication use. A full logistic regression model was used to identify factors predictive of osteoporosis medication use after a fracture or a diagnosis of osteoporosis.

RESULTS: The median length of follow-up from enrollment to the last WHI clinic visit for the study cohort was 13.9 years. Among the 13,990 women who reported new diagnoses of osteoporosis or fracture between enrollment and their final WHI visit, and also had medication data available, 21.6% reported taking an osteoporosis medication other than estrogen. Higher daily calcium intake, diagnosis of osteoporosis alone or both osteoporosis and fracture (compared with diagnosis of fracture alone), Asian or Pacific Islander race/ethnicity (compared with White/Caucasian), higher income, and hormone therapy use (past or present) were associated with significantly higher likelihood of osteoporosis pharmacotherapy. Women with Black/African American race/ethnicity (compared with White/Caucasian), body mass index $\geq$30 (compared with body mass index of 18.5-24.9), current tobacco use (compared with past use or lifetime nonusers), and history of arthritis were less likely to use osteoporosis treatment.

CONCLUSION: Despite well-established treatment guidelines in postmenopausal women with osteoporosis or history of fractures, pharmacotherapy use was suboptimal in this study. Initiation of osteoporosis treatment after fragility fracture may represent an opportunity to improve later outcomes in these high-risk women. Specific attention needs to be paid to increasing treatment among women with fragility fractures, obesity, current tobacco use, history of arthritis, or of Black race/ethnicity.

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KEYWORDS: Disparity; Fracture; Osteoporosis; Treatment

Osteoporosis is a key predisposing factor for fragility-type fractures that occur with minimal or low-impact trauma. Approximately 9 million osteoporotic fractures per year occur globally, most of which are observed in postmenopausal women.[1] The number of fractures is expected to increase as the population ages and lives longer. Osteoporotic fractures are associated with high morbidity, mortality, and cost.[2] The US Preventive Services Task Force

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recommends osteoporosis screening and treatment after a first fracture due to increased risk of future fractures, including a 20-fold greater risk for a clinically serious hip or spine fracture.[3,4] The National Osteoporosis Foundation considers all postmenopausal women and men older than 50 years with prior hip or vertebral fracture as candidates for osteoporosis treatment.[5] Their recommendations include calcium and vitamin D supplementation; regular weight-bearing, muscle strengthening, and balance-training exercises; and avoidance of tobacco and excess alcohol.[5] Bisphosphonates, an approved treatment for osteoporosis, reduce the risk for new fractures and mortality after hip fractures.[6-13]

Despite evidence supporting the impact of treating osteoporosis on reducing the incidence of recurrent fragility fractures, osteoporosis treatment is underutilized.[14-23] In a recent large observational cohort study, only 6.6% of hip fracture patients received calcium and vitamin D after surgery.[14] According to the 2008 Joint Commission Report, Improving and Measuring Osteoporosis Management, only 20% of patients with low-impact fractures in the general population are ever tested or treated for osteoporosis.[15] Previous studies suggest that sex, age, race, education level, insurance type, baseline calcium use, fracture site, prior osteoporosis diagnosis, previous fracture, chronic comorbidities, and history of cigarette smoking are predictors of use of osteoporosis medication for secondary prevention of further fractures.[24-29]

However, these studies have limitations, including short follow-up duration, not being population based, not being restricted to postmenopausal women, examining only one fracture site, and lack of information about vitamin D or calcium supplementation and lifestyle modifications.[14-29] Initiation of osteoporosis treatment after fragility fractures represents an opportunity to improve patient care. Identification and description of subject characteristics associated with likelihood of osteoporosis treatment is an important step in closing treatment gaps in postfracture intervention.

The goal of our study was to assess osteoporosis treatment and identify participant characteristics associated with treatment utilization after fracture or diagnosis of osteoporosis in the Women's Health Initiative (WHI). We hypothesized that osteoporosis treatment and recommended lifestyle modifications would occur in a low percentage of participants with fractures or diagnosis of osteoporosis. We also hypothesized that certain participant characteristics such as education level, age, and socioeconomic status would be associated with utilization of appropriate osteoporosis treatment.

CLINICAL SIGNIFICANCE

- A post hoc analysis of the Women's Health Initiative clinical trials data revealed suboptimal pharmacotherapy and recommended lifestyle modifications for osteoporosis treatment and fracture prevention among postmenopausal women with osteoporosis or history of fractures.
- Initiation of guideline-based osteoporosis treatment for fragility fracture may represent an opportunity to improve patient care. Specific attention needs to be paid to increasing treatment among patients with fragility fractures, obesity, current tobacco use, history of arthritis, or who are of black race.

METHODS

Setting

The WHI is a large, multicenter study designed to improve understanding of the determinants of major chronic diseases in postmenopausal women. Details of the study design, eligibility, and reliability of baseline measures have been described previously.[30,31] Women between 50 and 79 years of age and representing major racial/ethnic groups who were free from serious comorbidities were recruited from the general population at 40 clinical centers throughout the US between 1993 and 1998 into either the Clinical Trial (CT) (n = 68,132) or the Observational Study component (n = 93,676).[30,31] The CT enrolled participants into one or more randomized controlled clinical trial components: the Hormone Therapy (HT) Trials of estrogen alone or estrogen plus progestin, the low-fat Dietary Modification Trial (DM), and the Calcium/Vitamin D supplementation Trial (CAD).[30] After the main study closeout from 2004-2005, participants were offered the opportunity to continue an additional 5 years in the WHI Extension Study, during which yearly health update questionnaires were administered by mail between 2005 and 2010.[31]

Analytic Cohort

Among the 68,132 women initially enrolled in the CT, we excluded the treatment group of HT and included participants assigned to the control group of the HT trial (n = 13,531) and women only in the CAD or DM trials (n = 40,785; total n = 54,316). We excluded participants with self-reported osteoporosis at baseline enrollment, personal fracture after age 55 years, or use of osteoporosis treatment other than estrogen at enrollment, as well as those with missing values for important covariables (**Figure 1**). We then further excluded participants without subsequent incident self-reported osteoporosis or fracture between enrollment and their last WHI clinic visit. Our final analytic cohort included 17,803 participants not receiving osteoporosis treatment at baseline who reported an incident fracture or diagnosis of osteoporosis in the time period between enrollment and final WHI visit who would be eligible for osteoporosis treatment.

The fracture outcomes for this analysis include hip, clinical spine, forearm, wrist, and total fractures (excluding ribs, sternum, skull, face, fingers, toes, and cervical vertebrae) that occurred after enrollment. We defined

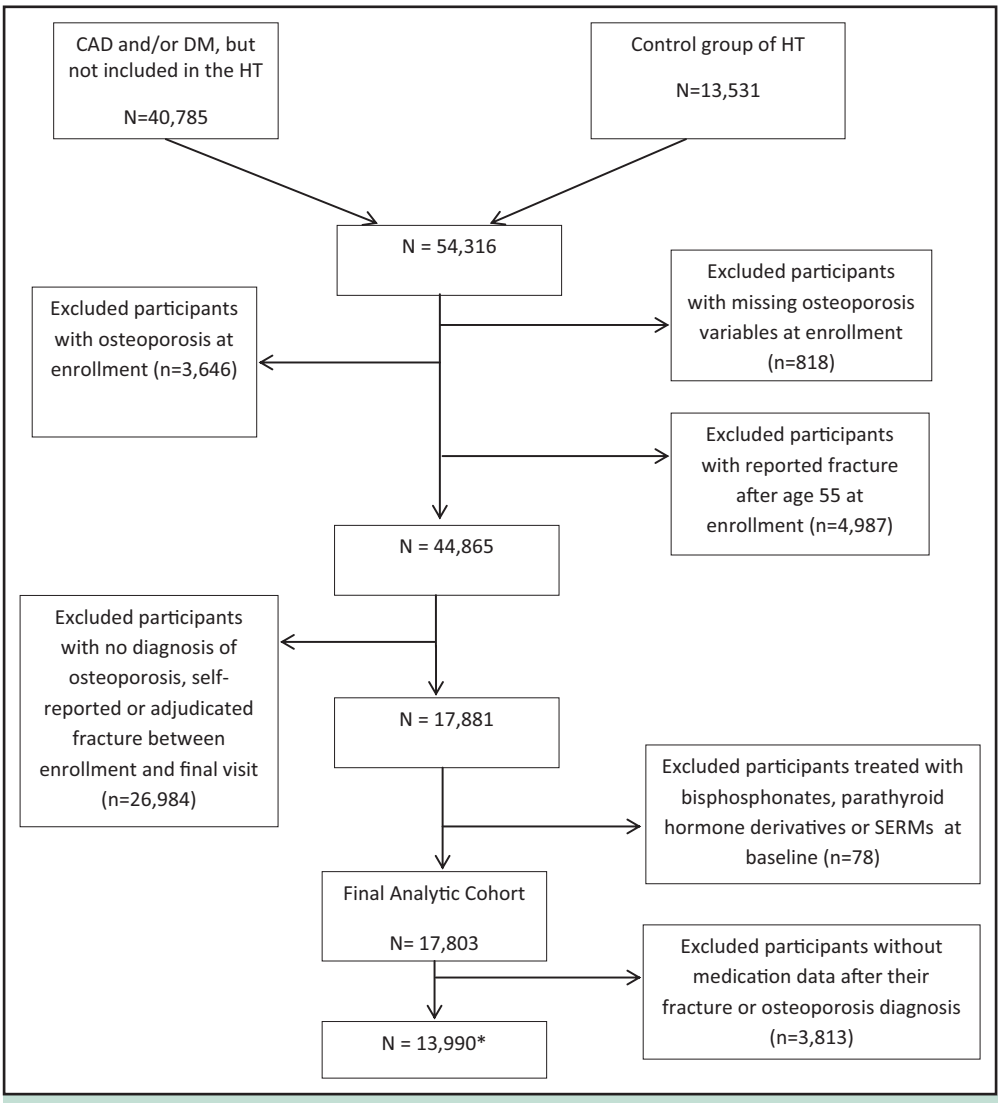

Figure 1 STROBE Flow Diagram of Analytic Cohort (n = 17,803) with inclusion and exclusion criteria. CAD = Calcium/Vitamin D supplementation Trial; CT = clinical trial; DM = Dietary Modification Trial; HT = hormone therapy; SERMs = selective estrogen receptor modulators. *Participants in the final analytic cohort with medication data available after their fracture or osteoporosis diagnosis.

osteoporosis treatment as use of one of the US Food and Drug Administration (FDA)-approved medications available during the study period to treat osteoporosis: bisphosphonates (eg, alendronate, ibandronate, risedronate, etidronate, and zoledronic acid), recombinant human parathyroid hormone (teriparatide, rhPTH), calcitonin, selective estrogen receptor modulators ([SERMs], eg, raloxifene), or any combination thereof. Denosumab was not approved until 2010 for treatment of postmenopausal osteoporosis and was not included in this study. While not FDA-approved for osteoporosis treatment, we did include tamoxifen because of data suggesting efficacy in fracture prevention in postmenopausal women.[32,33] We did not include estrogen/hormone therapy as osteoporosis treatment, but recognized that hormone therapy might have been used as osteoporosis pharmacotherapy and therefore, stratified the analysis by hormone therapy use and excluded participants randomized to the treatment arm of HT. Vitamin D and calcium intake were considered as lifestyle modifications and adjuncts to pharmacotherapy. Other lifestyle modifications examined included amount of physical activity, tobacco use, and alcohol intake.

Data Collection, Follow-Up, and Outcome Ascertainment

Self-administered questionnaires were completed at study entry to collect information on demographics; medical,

reproductive, and family history; current health status; number of falls during the past 12 months; and dietary and lifestyle factors.[30,31] Total recreational physical activity energy expenditure (metabolic equivalent hours per week) was computed from self-reported time spent in various lifestyle and leisure activities and walking.[34] Trained staff used standardized protocols to measure weight, height, and waist and hip circumferences for all participants at enrollment. Questionnaires assessing depressive symptoms, optimism, and cynical hostility were administered at enrollment.[35,36] Data on medications were verified by asking participants to bring all medications, vitamins, and supplements to the clinic at enrollment.[30,31] In addition, medication data were collected during enrollment and follow-up years 1, 3, 6, and 9, as well as extension years.[37,38]

During follow-up, participants were asked if they were prescribed medication for treatment or prevention of "osteoporosis or other bone conditions," and if a doctor had diagnosed them with osteoporosis for the first time since their last study visit or told them that they "had a new broken, crushed, or fractured bone?" Participants were asked which bone they broke, with response choices of: hip, upper leg (not hip), pelvis, knee (patella), lower leg or ankle, foot (not toe), spine or back (vertebra), lower arm or wrist, hand (not finger), elbow, and upper arm or shoulder. Clinical outcomes were self-reported semiannually in the CT.[39] Participants reporting a hip fracture were contacted for additional information and medical records, and these events were centrally adjudicated by trained physician adjudicators.[39,40] Non-hip fractures were also adjudicated by trained physician adjudicators' review of medical records during the main trial, but were based on only self-report during the extension.[39-41]

Statistical Analysis

We used SAS statistical software (version 9.3; SAS Institute Inc, Cary, NC) to perform analysis of the data. Participants were categorized as "Fracture Only," "Self-Reported Diagnosis of Osteoporosis Only," or "Both Fracture and Diagnosis of Osteoporosis." Participants with fracture were further categorized as "Hip Fracture," "Clinical Vertebral Fracture," or "Other Fracture." Characteristics of the groups were compared with analysis of variance (continuous variables) and chi-squared tests (categorical variables) (**Table 1**). The pattern of percentage of use of osteoporosis medication as well as calcium supplementation, vitamin D supplementation, and estrogens (oral or transdermal) were computed for each study year with available medication data (**Table 2**). Analyses of visits prior to and immediately subsequent to the first fracture event or osteoporosis diagnosis were evaluated for medication use, including and excluding hormone therapy (estrogen, oral, or transdermal) among the women with available medication data (**Table 3**). Similarly, analyses of visits prior to and immediately subsequent to the first fracture event were evaluated for medication use among the women with available medication data by different types of fracture (**Table 4**). We investigated changes in alcohol consumption, smoking behavior, exercise, and supplementation with vitamin D and calcium for participants with available behavior data after their fracture or osteoporosis diagnoses (**Table 5**). Comparisons between prior and subsequent visits were made using paired *t*-tests (continuous variables) or McNemar test (binary variables) in analyses stratified by hormone therapy use. A full logistic regression model that included relevant variables identified from literature review was used to identify variables predictive of osteoporosis medication use after a fracture or a diagnosis of osteoporosis (**Figure 2**). We also identified variables predictive of osteoporosis medication use after different types of fractures (**Table 4**). A level of significance of .05 was used for all analyses.

RESULTS

Of the 17,803 women who reported a new diagnosis of osteoporosis or fracture in the interval between enrollment and their final WHI visit, 3457 reported both fracture and new diagnosis of osteoporosis, 7926 only fracture, and 6420 only new diagnosis of osteoporosis (**Table 1**). The median length of follow-up from enrollment to the last WHI clinic visit for the study cohort was 13.9 years (SD 3.3; range 0.5-18.9). Age of participants at enrollment ranged from 50 to 79 years, with a mean age of 63 years (**Table 1**). At the time of enrollment, 31% of participants reported taking estrogen, 24% calcium supplementation, and 4% vitamin D (**Table 2**). Over the study period, the number of participants taking bisphosphonates, calcitonin, and SERMs increased, while the number of participants reporting hormone therapy use decreased. Fewer data points were available for year 9 of the study because the main trial ended that year. Only 13,990 (78.6%) participants had medication data available for the first study visit after the diagnosis of osteoporosis or fracture (**Table 3**). When considering pharmacotherapies other than hormone therapy, calcium, and vitamin D, appropriate osteoporosis medication use was reported more frequently in visits subsequent to diagnosis of osteoporosis only (31.7%) and diagnoses of both osteoporosis and fracture (29.4%), compared with diagnosis of fracture only (5.2%). This pattern was consistent when hormone therapy was included for participants who were not on hormone therapy at baseline. Among participants with fracture, osteoporosis medication use was higher in the groups with hip (19.8%) and vertebral (20.2%) fractures compared with the group with other fractures (14%) ($P < .0001$) (**Table 4**).

Table 5 summarizes the pattern of behavioral changes among participants with available behavior data after diagnosis of osteoporosis, fracture, or both. While mean reported alcohol intake decreased across all groups, the

Table 1 Baseline Characteristics of Women's Health Initiative Participants with Indications for Secondary Osteoporosis Prevention (N = 17,803)

	Indication for Secondary Osteoporosis Prevention				
Characteristic n (%)	All (n = 17,803)	Fracture Only (n = 7926)	Osteoporosis Only (n = 6420)	Fracture and Osteoporosis (n =3457)	*P*-Value
I. Sociodemographic					
Age at screening, mean (± SD), y	62.6 (6.9)	61.9 (7.0)	62.6 (6.8)	63.9 (7.0)	<.0001*
US residency region					.0167*
Northeast	4511 (25.3)	1918 (24.2)	1651 (25.7)	942 (27.3)	
South	4424 (24.9)	1986 (25.1)	1596 (24.9)	842 (24.4)	
Midwest	3831 (21.5)	1700 (21.5)	1392 (21.7)	739 (21.4)	
West	5037 (28.3)	2322 (29.3)	1781 (27.7)	934 (27.0)	
Race/ethnicity, n (%)					<.0001*
American Indian/Alaskan Native	71 (0.4)	32 (0.4)	29 (0.5)	10 (0.3)	
Asian/Pacific Islander	399 (2.3)	119 (1.5)	212 (33.1)	68 (2.0)	
Black/African American	1327 (7.5)	661 (8.4)	527 (8.2)	139 (4.0)	
Hispanic/Latino	614 (3.5)	201 (2.5)	307 (4.8)	106 (3.1)	
White (not Hispanic origin)	15,158 (85.3)	6814 (86.1)	5248 (82.0)	3096 (89.8)	
Unknown	196 (1.1)	86 (1.1)	81 (1.3)	29 (0.8)	
Education level, n (%)					.0011*
≤High school/GED	3903 (22.1)	1631 (20.7)	1521 (23.8)	751 (21.8)	
School after high school	6912 (39.1)	3078 (39.1)	2464 (38.6)	1370 (39.8)	
≥College degree	6887 (38.9)	3165 (40.2)	2404 (37.6)	1318 (38.3)	
Annual family income, $, n (%)					.0590
≤20,000	2533 (14.2)	1081 (13.6)	937 (14.6)	515 (14.9)	
>20,000	14,252 (80.1)	6409 (80.9)	5085 (79.2)	2758 (79.8)	
Don't know	393 (2.3)	177 (2.3)	143 (2.3)	73 (2.2)	
Marital status, n (%)					.0095*
Never married	694 (3.9)	323 (4.1)	238 (3.7)	133 (3.9)	
Divorced or separated	2701 (15.2)	1233 (15.6)	986 (15.4)	482 (14.0)	
Widowed	2834 (16.0)	1252 (15.8)	966 (15.1)	616 (17.9)	
Presently married	11,192 (63.1)	4943 (62.6)	4902 (64.1)	2157 (62.7)	
Marriage-like relationship	309 (1.7)	151 (1.9)	104 (1.6)	54 (1.6)	
Any insurance	16,853 (95.4)	7496 (95.3)	6046 (94.9)	3311 (96.4)	.0025*
II. Lifestyle					
Smoking, n (%)					.3403
Never	8882 (50.5)	3913 (49.9)	3238 (51.1)	1731 (50.7)	
Past	7424 (42.2)	3370 (43.0%)	2620 (41.3)	1434 (42.0%)	
Current	1293 (7.4)	559 (7.1)	484 (7.6)	250 (7.3)	
BMI, kg/m^2, mean, n (%)	28.3	29.3	27.5	27.5	<.0001*
<18.5	86 (0.5)	23 (0.3)	39 (0.6)	24 (0.7)	
18.5-<25.0	5392 (30.3)	1855 (23.4)	2326 (36.2)	1211 (35.0)	
25.0-<30.0	6507 (36.6)	2918 (36.8)	2312 (36.0)	1277 (37.2)	
≥30.0	5733 (32.2)	3096 (39.1)	1714 (26.7)	923 (26.7)	
Alcohol intake, drinks/week, n (%)					.2099
0/past drinker	7209 (40.5)	3126 (39.4)	2671 (41.6)	1412 (40.8)	
>0-<14	10,004 (56.2)	4535 (57.2)	3538 (55.1)	1931 (55.9)	
≥14	512 (2.9)	234 (3.0)	182 (2.8)	96 (2.8)	
Total recreational physical activity (MET-hours/week), mean, (range)	10.7 (0-124.8)	10.6 (0-121.3)	10.7 (0-124.8)	11.0 (0-98.0)	.3746
III. Health and health care					
Self-rate health status, n (%)					.0075*
Excellent	2692 (16.7)	1275 (16.1)	1161 (18.2)	526 (15.3)	
Very good	7411 (41.8)	3283 (41.6)	2650 (41.5)	1478 (42.9)	
Good	5973 (33.7)	2729 (34.6)	2080 (32.6)	1164 (33.8)	
Fair/poor	1375 (7.8)	611 (7.7)	489 (7.7)	275 (8.0)	

Table 1 Continued

Characteristic n (%)	Indication for Secondary Osteoporosis Prevention				
	All (n = 17,803)	Fracture Only (n = 7926)	Osteoporosis Only (n = 6420)	Fracture and Osteoporosis (n =3457)	*P*-Value
Current health care provider, n (%)	16,550 (93.7)	7380 (93.9)	5945 (93.3)	3225 (94.0)	.2376
Primary Care Provider visit in past year, n (%)	14,048 (81.5)	6318 (82.2)	4978 (80.2)	2752 (82.1)	.0040*
Time since last medical visit, mo, mean (range)	6.4 (0-376.8)	6.3 (0-376.8)	6.6 (0-185.4)	6.3 (0.1-130.2)	.2450
Mammogram, ever, n (%)	17,185 (96.9)	7663 (97.0)	6193 (96.8)	3329 (96.7)	.5899
Pap smear, ever, n (%)	15,193 (98.2)	6792 (98.4)	5550 (97.9)	2914 (98.3)	.2944
IV. Medication use					
Hormone use, n (%)					<.0001*
Never	8093 (45.5)	3365 (42.5)	3039 (47.4)	1689 (49.0)	
Past	2915 (16.4)	1200 (15.2)	1092 (17.0)	623 (18.1)	
Current	6771 (38.1)	3350 (42.3)	2284 (35.6)	1137 (33.0)	
Number of medications, mean (range)	2.9 (1-23)	3.1 (1-21)	2.7 (1-24)	2.9 (1-20)	<.0001*
Total calcium intake, mean (± SD), mg/day	1113.7 (674.9)	1114.3 (672.1)	1108.3 (675.9)	1122.5 (679.3)	.6056
<600	3940 (22.2)	1711 (21.7)	1496 (23.4)	713 (21.3)	
600-<800	2766 (15.6)	1251 (15.8)	960 (15.0)	555 (16.1)	
800-<1200	4621 (26.0)	2047 (25.9)	1665 (26.0)	909 (26.4)	
≥1200	1248 (39.2)	2890 (36.6)	2274 (35.6)	1248 (36.2)	
Dietary calcium intake (mg/day), mean (range)	812.5 (0.07-6935.8)	829.9	790.9	812.8	<.0001*
<600	35.9 (6375)	34.2 (2702)	38.2 (2457)	35.3 (1216)	
600-<800	21.9 (3878)	22.1 (1747)	21.0 (1344)	22.8 (787)	
800-<1200	26.0 (4603)	26.1 (2060)	25.7 (1642)	26.2 (901)	
≥1200	16.3 (2883)	17.6 (1390)	14.9 (952)	15.7 (541)	
Total vitamin D intake (food and supplements), mean (± SD), IU/day	348.4 (264.6)	347.8 (264.3)	346.3 (268.2)	353.7 (258.2)	.4068
<200	7221 (40.7)	3211 (40.7)	2647 (41.4)	1363 (39.6)	
200-≤400	3465 (19.5)	1580 (20.0)	1201 (18.8)	684 (19.9)	
>400	7053 (39.8)	3108 (39.4)	2547 (39.8)	1398 (40.6)	
Dietary vitamin D intake (μg), mean (range)	4.3 (0-35.31)	4.4	4.2	4.4	<.0001*
<200	69.9 (12,407)	68.5 (5410)	71.9 (4596)	69.7 (2401)	
≥200	30.1 (5332)	31.5 (2489)	28.1 (1799)	30.3 (1044)	
Activity of daily living disability, n (%)					.0018*
No assistance	14,786 (98.6)	6508 (98.2)	5447 (99.0)	2831 (98.5)	
Needs assistance (ADL ≥1)	214 (1.4)	117 (1.8)	55 (1.0)	42 (1.5)	
Number of falls in previous 12 mo, n (%)					<.0001*
None	10,666 (59.9)	4543 (57.3)	4122 (64.2)	2001 (57.9)	
1	3327 (18.7)	1556 (19.6)	1106 (17.2)	665 (19.2)	
≥2	2202 (12.4)	1077 (13.6)	656 (10.2)	469 (13.6)	
V. Comorbidities, n (%)					
Congestive heart failure	456 (2.6)	219 (1.2)	139 (0.8)	98 (0.6)	.0414*
Cardiovascular disease	2581 (16.5)	1185 (7.6)	878 (5.6)	518 (3.3)	.0112*
Arthritis	8104 (45.9)	3691 (20.9)	2721 (15.4)	1692 (9.6)	<.0001*
Emphysema	561 (3.6)	218 (1.4)	219 (1.4)	124 (0.8)	.0268*
Hypertension	5764 (32.6)	2797 (15.8)	1944 (11.0)	1023 (5.8)	<.0001*
History of cancer	749 (4.3)	325 (1.8)	260 (1.5)	164 (0.9)	.2045
Hip replacement	199 (1.3)	98 (0.6)	50 (0.3)	51 (0.3)	.0017*
Other joint replacement	343 (2.2)	197 (1.3)	80 (0.5)	66 (0.42)	<.0001*
Depressed mood	1890 (10.9)	883 (11.4)	631 (10.1)	376 (11.2)	.0348*
Optimism group					.0239*

Table 1 Continued

Characteristic n (%)	All (n = 17,803)	Indication for Secondary Osteoporosis Prevention: Fracture Only (n = 7926)	Osteoporosis Only (n = 6420)	Fracture and Osteoporosis (n =3457)	*P*-Value
Mid-high & most optimistic	8409 (48.2)	3839 (49.4)	2978 (47.5)	1592 (47.0)	
Mid-low & least optimistic	9032 (51.8)	3940 (50.7)	3296 (52.5)	1796 (53.0)	
Cynical hostility					.8275
Mid-high & most hostile	674 (3.8)	306 (3.9)	243 (3.8)	125 (3.6)	
Mid-low & least hostile	16,992 (96.2)	7570 (96.1)	6117 (96.2)	3305 (96.4)	
VI. CAD trial status, n (%)					<.0001*
Not randomized to CAD trial	8351 (46.9)	3522 (44.4)	3165 (49.3)	1664 (48.1)	
Calcium − vitamin D arm of CAD	4723 (26.5)	2180 (27.5)	1661 (25.9)	882 (25.5)	
Control arm of CAD	4729 (26.6)	2224 (28.1)	1594 (24.8)	911 (26.4)	

Activity of daily living (ADL) disability = needing assistance with one or more of ADLs; BMI = body mass index; CAD Trial = Calcium/Vitamin D Supplementation Trial; GED = general equivalency degree; MET = metabolic equivalent; SD = standard deviation.
*Statistically significant *P*-values.

change was statistically significant only for the entire study cohort and the fracture-only subgroup. The percentage of current smokers was low at baseline, decreased across all groups, and was significantly reduced in the entire study cohort and osteoporosis-only subgroup. Self-reported physical activity decreased and body mass index (BMI) increased across all study groups. While BMI changes were statistically significant for all groups, the differences in physical activity patterns were statistically significant for only the entire study cohort and the fracture-only subgroup. All groups except the subgroup of both osteoporosis and fracture reported taking calcium supplementation less frequently after the diagnosis of fracture or osteoporosis, and the changes were significant for the entire cohort, the fracture-only subgroup, and the osteoporosis-only subgroup. While more participants reported taking vitamin D supplement in the entire cohort, the osteoporosis-only subgroup, and the subgroup with both osteoporosis and fracture, fewer participants in the fracture-only subgroup reported vitamin D use after the fracture. The changes in vitamin D supplementation were statistically significant for the entire cohort and the subgroup with both osteoporosis and fracture.

We found a statistically significant association between appropriate osteoporosis treatment, other than estrogen, and the following variables: diagnosis group, race/ethnicity, income, BMI, smoking status, history of arthritis, hormone use status, and total (dietary and supplemental) daily calcium intake (**Figure 2**). Having a diagnosis of osteoporosis, either alone or in combination with a diagnosis of fracture, was associated with almost 5 times higher likelihood of being on treatment medication compared with diagnosis of fracture only. Asian or Pacific Islander race/ethnicity was associated with 45.1% higher likelihood of being on treatment medication compared with White/Caucasian, while Black/African American was associated with almost half the likelihood of appropriate medication use. Higher income was associated with higher likelihood of being on treatment medication. Having a BMI of 30 or higher, compared with BMI of 18.5-24.9, was associated with 39.9% reduction in medication use. Current tobacco use was associated with approximately 30% reduction in appropriate pharmacotherapy, compared with lifetime nonsmokers and previous smokers. Reporting a history of arthritis was associated with 15.6% less likelihood of osteoporosis medication use. Never having been on hormone therapy was associated with approximately 20% lower likelihood of osteoporosis medication use compared with current or previous hormone treatment. While ever hormone therapy use was associated with higher likelihood of use of all medication categories, the association was statistically significant only for calcitonin and SERMs (data not shown). Women reporting daily calcium intake of 1200 mg or more, compared with <600 mg daily, were 23.2% more likely to report osteoporosis pharmacotherapy.

Diagnosis of osteoporosis, higher income, past or current hormone therapy use, and higher total daily calcium (dietary and supplemental) intake were also associated with statistically significant higher likelihood of osteoporosis medication use among participants with fractures (**Table 4**). BMI of 30 or higher, compared with BMI of 18.5-24.9, was associated with lower likelihood of osteoporosis treatment after a fracture. We did not find a statistically significant relationship between appropriate osteoporosis treatment and the following variables: age, optimism, negativity, cynical hostility, depression, education level, alcohol intake, activities of daily living construct, total recreational physical activity, total daily vitamin D intake, number of medications, insurance status, having a care provider, primary care provider visit in the past year, time since provider last seen, general health, number of falls, disability, marital status, occupation, history of cardiovascular disease, replacement of hips or other joints, or preventive measures such as cervical and breast cancer screening.

Table 2 Number (%) of Participants at Each Study Visit who Reported Taking Osteoporosis Medication

Drug Class	Baseline (n = 17,803)	Year 1 (n = 17,636)	Year 3 (n = 17,416)	Year 6 (n = 17,372)	Year 9 (n = 15,451)	Extension: Years 12-17 (n = 15,251)
Bisphosphonates	0 (0)	310 (1.8)	1056 (6.1)	2805 (16.2)	934 (6.0)	2872 (18.8)
PTH	0 (0)	0 (0)	0 (0)	2 (0.01%)	3 (0.02)	38 (0.3)
Calcitonin	0 (0)	46 (0.3)	181 (1.0)	229 (1.32%)	61 (0.4)	71 (0.5)
Estrogen (oral or transdermal)	5441 (30.6)	5837 (33.1)	6074 (34.9)	4145 (23.7)	597 (3.9)	943 (6.2)
SERMs	0 (0)	49 (0.3)	362 (2.1)	774 (4.5)	209 (1.4)	401 (2.6)
Calcium supplement	4267 (24.0)	3922 (22.2)	3532 (20.3)	3422 (19.7)	888 (5.8)	8033 (52.7)
Vitamin D supplement	644 (3.6)	800 (4.5)	803 (4.6)	1023 (5.9)	322 (2.1)	1356 (8.9)
Any treatment meds (excluding calcium and vitamin D supplement)	5441 (30.6)	6134 (34.8)	7196 (41.3)	7206 (41.5)	1623 (10.5)	4055 (26.6)

PTH = parathyroid hormone derivatives; SERMs = selective estrogen receptor modulators.

DISCUSSION

Despite well-established guidelines for fracture prevention in postmenopausal women with osteoporosis or fractures,[3,5] calcium and vitamin D supplementation, behavior changes, and pharmacotherapy were suboptimal in WHI participants who reported an incident fracture or new diagnosis of osteoporosis during the study. Only 21.6% of participants who suffered an incident fracture or were diagnosed with osteoporosis during the study reported taking medications other than estrogen to treat osteoporosis and prevent future fractures. Even when we included hormone therapy as possible pharmacotherapy for osteoporosis in participants not on hormone therapy at baseline, treatment rate increased to only 27.9%. Furthermore, while there was a small decrease in tobacco and alcohol use after diagnosis of fracture or osteoporosis, there was also a decrease in the reported amount of total recreational physical activity and an increase in BMI, which could, in part, reflect aging of the study population.

We identified characteristics of participants associated with likelihood of osteoporosis treatment after fracture or osteoporosis diagnosis in a large, ethnically and geographically diverse cohort of postmenopausal women in the US. Previous studies have reported associations between osteoporosis treatment and the following variables: fracture site, prior osteoporosis diagnosis, previous fracture, baseline

Table 3 Number (%) of Medication Use after Diagnosis of Osteoporosis or Fracture (n = 13,315)

Hormone Therapy Before* Diagnosis of Osteoporosis or Fracture	All (n = 3986)	Fracture Only (n = 1472)	Osteoporosis Only (n = 1643)	Osteoporosis and Fracture (n = 871)	*P*-Value
Drug class					
Bisphosphonates	700 (17.6)	49 (3.3)	438 (26.7)	213 (24.5)	<.0001
PTH	0 (0)	0 (0)	0 (0)	1 (0.1)	NA
Calcitonin	74 (1.9)	5 (0.3)	44 (2.7)	25 (2.9)	<.0001
Estrogen (oral or transdermal)	2218 (55.6)	833 (56.6)	856 (52.1)	529 (60.7)	.0001
SERMs	105 (2.6)	24 (1.6)	28 (3.5)	23 (2.6)	.0042
Any treatment	2613 (65.6)	883 (60.0)	1094 (66.6)	636 (73.0)	<.0001
Treatment medications excluding hormone therapy	853 (21.4)	76 (5.2)	521 (31.7)	256 (29.4)	<.0001
No hormone therapy before diagnosis of osteoporosis or fracture	(n = 10,004)	(n = 3292)	(n = 4241)	(n = 2471)	
Bisphosphonates	1696 (17.0)	124 (3.8)	1014 (23.9)	558 (22.6)	<.0001
PTH	0 (0)	0 (0)	0 (0)	0 (0)	NA
Calcitonin	175 (1.8)	14 (0.4)	87 (2.1)	74 (3.0)	<.0001
Estrogen (oral or transdermal)	804 (8.0)	187 (5.7)	380 (9.0)	237 (9.6)	<.0001
SERMs	361 (3.6)	60 (1.8)	193 (4.6)	108 (4.4)	<.0001
Any treatment	2792 (27.9)	370 (11.2)	1536 (36.3)	886 (35.9)	<.0001
Treatment medications excluding hormone therapy	2162 (21.6)	192 (5.8)	1259 (29.7)	711 (28.8)	<.0001

There were 158 participants missing a "before" hormone therapy value.

*Before = the time point immediately before diagnosis of osteoporosis or fracture; PTH = parathyroid hormone derivatives; SERMs = selective estrogen receptor modulators.

Table 4 Number (%) of Medication Use after Diagnosis of Fracture (n = 11,383) and Variables Associated with Treatment

	All Fractures	Hip Fractures	Clinical Vertebral Fractures	All Other Fractures	*P*-Value
Total number	11,383	874 (7.7%)	1407 (12.4%)	9102 (80.0%)	
Number with osteoporosis	3457 (30.4%)	343 (39.2%)	605 (43%)	2509 (27.6%)	
Number with available data	8183 (71.9%)	628 (71.9%)	1044 (74.2%)	6511 (71.5%)	
Number treated	1244 (15.2%)	124 (19.8%)	211 (20.2%)	909 (14%)	<.0001
Number treated including estrogen (oral or transdermal)	2792 (34.1%)	212 (33.8%)	390 (37.4%)	2190 (33.6%)	.0614
Odds ratio of treatment (CI)					
Presence of osteoporosis	4.9 (4.2-5.7)	6.5 (3.6-11.9)	4.6 (2.9-7.2)	4.8 (4.0-5.7)	
Income ≥20,000	1.3 (1.1-1.6)		2.0 (1.1-3.4)	1.3 (1.0-1.7)	
BMI ≥30 vs BMI = 18.5-24.9	0.7 (0.6-0.8)		0.5 (0.3-0.9)	0.7 (0.5-0.8)	
Past HT use	1.2 (1.0-1.5)			1.3 (1.0-1.6)	
Current HT use	1.9 (1.6-2.3)			2.0 (1.6-2.5)	
Total daily calcium intake of 800-1199 mg vs <600 mg	1.3 (1.0-1.6)				
Total daily calcium intake ≥1200 mg vs <600 mg daily	1.4 (1.2-1.7)		2.05 (1.2-3.6)	1.4 (1.1-1.8)	

The fracture outcomes for this analysis include hip, clinical spine, forearm, wrist, and total fractures (excluding ribs, sternum, skull, face, fingers, toes and cervical vertebrae) that occurred after enrollment. We defined osteoporosis treatment as use of one of the following medications: bisphosphonates (eg, alendronate, ibandronate, risedronate, etidronate, and zoledronic acid), recombinant parathyroid hormone (teriparatide, rhPTH), calcitonin, selective estrogen receptor modulators, (eg, raloxifene, tamoxifen), or any combination thereof.

BMI = body mass index; CI = confidence interval; HT = hormone therapy.

calcium use, age, race, education level, insurance type, chronic comorbidities, and history of cigarette smoking.[24-29] In the present study, we did not find an association between osteoporosis pharmacotherapy and participants' age, education level, or insurance type. However, consistent with previous literature, we observed statistically significant associations between pharmacotherapy for osteoporosis and baseline total calcium intake, prior osteoporosis diagnosis, fracture site, and smoking status. We also identified other characteristics associated with higher likelihood of osteoporosis pharmacotherapy, including Asian or Pacific Islander race/ethnicity (compared with being white/Caucasian), higher income, and past or present hormone therapy use. Participant characteristics associated with lower osteoporosis medication use included black/African American race/ethnicity (compared with being white/Caucasian), baseline BMI of 30 or greater (compared with BMI of 18.5-24.9), current tobacco use (compared with past use or lifetime nonusers), and history of arthritis. The lower treatment rates among black/African American women are consistent with the lower risk of fracture among these women.[42] For women with BMI of 30 or greater, the lower treatment rates might reflect the historical belief that obesity is protective against osteoporosis and fractures,[43,44] although recent studies suggest that obesity is not protective against fractures in postmenopausal women.[45] The extent that perceived benefit of obesity against fracture risk is influencing utilization of osteoporosis medication use remains unclear. The relatively lower use of such therapy in obese women compared with their nonobese counterparts might also reflect generally poorer health habits often seen in obese adults.[46]

Strengths of our study include its long duration of follow-up, inclusion of a large, socioeconomically, ethnically, and geographically diverse cohort of postmenopausal women in the US, physician adjudication of fracture events, and available data on potentially important factors, including physical activity, medications, and psychological attitudes. However, one important limitation to our study is the lack of availability of study entry year for individual participants and the possibility that some of the medications studied had not been FDA approved for clinical use. While we excluded denosumab from our analysis because it was not approved until 2010 for postmenopausal osteoporosis, we did include medications such as alendronate (approved in 1995), intranasal calcitonin (approved in 1995), and raloxifene (approved in 1997), which would have been available for most of the WHI duration. Furthermore, the use of zoledronic acid might have been under-reported, as it is a medication not administered at home. We noted a decrease in treatment rates at year 9 of the study, but also had fewer data points for this year because the main trial ended that year. While we do not have access to enrollment year for individual participants, we know that enrollment occurred between 1993 and 1998, and therefore, study year 9 would have been between 2002 and 2007. Therefore, the safety concerns about bisphosphonates might have contributed to the decrease in bisphosphonate use only for the later enrollees.[47,48] Another limitation is the lack of information about medical decisions and medication prescriptions from participants' health care providers if not reported by participants. Thus, we are not able to identify whether the barrier to osteoporosis treatment is at the provider level or in the participant's willingness to accept this type of therapy and therefore, cannot address the important question of whether

Table 5 Pattern of Behavioral Changes Following a Fracture or Diagnosis of Osteoporosis

Behavior	All	*P*-Value	Fracture Only	*P*-Value	Osteoporosis	*P*-Value	Osteoporosis and Fracture	*P*-Value
Alcohol		<.0001*		.0134*		.1521		.1142
N	8540		2564		3812		2164	
Servings per week, mean (± SD)								
Before	1.9 (4.0)		1.99 (3.9)		1.87 (4.3)		1.82 (3.6)	
After	1.8 (3.8)		1.83 (3.9)		1.79 (3.6)		1.72 (3.8)	
Change	−0.11 (3.3)		−0.16 (3.3)		−0.08 (3.5)		−0.10 (2.9)	
Total recreational physical activity (MET-hours/week)		.0028*		.0009*		.7970		.0641
N	8567		2571		3283		2173	
Mean (± SD)								
Before	12.1 (13.5)		12.1 (14.2)		12.0 (13.0)		12.1 (13.4)	
After	11.7 (12.9)		11.3 (13.2)		11.9 (12.8)		11.6 (12.9)	
Change	−0.39 (12.2)		−0.84 (12.7)		−0.05 (11.9)		−0.5 (11.9)	
BMI, kg/m^2		<.0001*		.0010*		.0019*		<.0001*
N	9862		3151		4074		2637	
Mean (± SD)								
Before	27.8 (5.6)		29.2 (5.8)		27.1 (5.4)		27.3 (5.3)	
After	28.0 (5.7)		29.4 (5.8)		27.2 (5.5)		27.6 (5.6)	
Change	+0.2 (2.9)		+0.2 (2.9)		+0.1 (2.8)		+0.2 (2.9)	
Currently smoking		<.0001*		.0851		.0005*		.0796
N	8063		2404		3640		2019	
n (%)								
Before	500 (6.2)		145 (6.0)		235 (6.5)		120 (5.9)	
After	442 (5.5)		132 (5.5)		203 (5.6)		107 (5.3)	
Vitamin D supplement		.0234*		.2813		.0748		.0013*
N	13,990		4764		5884		3342	
n (%)								
Before	629 (4.5)		192 (4.0)		285 (4.8)		152 (4.6)	
After	704 (5.0)		173 (3.6)		325 (5.5)		206 (6.2)	
Calcium supplement		<.0001*		<.0001*		<.0001		.4297
N	13,999		4771		5884		3344	
n (%)								
Before	2906 (20.8)		869 (18.2)		1300 (22.1)		737 (22.0)	
After	2614 (18.7)		699 (14.6)		1156 (19.7)		759 (22.7)	

BMI = body mass index; MET = metabolic equivalent; SD = standard deviation.
*Statistically significant *P*-values.

future intervention to optimize osteoporosis treatment should target health care providers, patients, or both. Additionally, as noted in Table 2, the use of hormone therapy decreased significantly over the course of the study. This finding likely reflects physicians' and patients' developing awareness of risks and benefits of hormone therapy due to dissemination of WHI HT findings and resulting changes in physicians' recommendations, prescription practices, and individual acceptance of hormone therapy. Also, our study might have missed participants who started and then stopped an osteoporosis medication between 2 study years, thereby potentially underestimating initial medication use. Furthermore, because we did not have detailed historical information about circumstances of the fractures, we cannot determine which fractures were truly fragility or low-impact fractures. Finally, we could not confirm the self-reported diagnosis of osteoporosis because bone mineral density was measured at only 3 WHI clinics and we did not have data about bone mineral density measurements performed outside of the study. While self-reported prevalent osteoporosis has been demonstrated to have moderate-to-good validity, self-reported incident osteoporosis has only poor-to-moderate validity in middle-aged and older women.[49] It is possible that some participants who self-reported new diagnosis of osteoporosis might have been diagnosed with osteopenia instead and therefore, were not candidates for osteoporosis treatment. Furthermore, it is possible that treatment thresholds were not achieved for at least some of the younger participants with non-hip and non-vertebral fractures, which might have affected the lower treatment rates among this group.

CONCLUSIONS

The treatment for osteoporosis was suboptimal among the WHI women with incident fractures or a diagnosis of osteoporosis. In fact, only 21.6% of these high-risk women

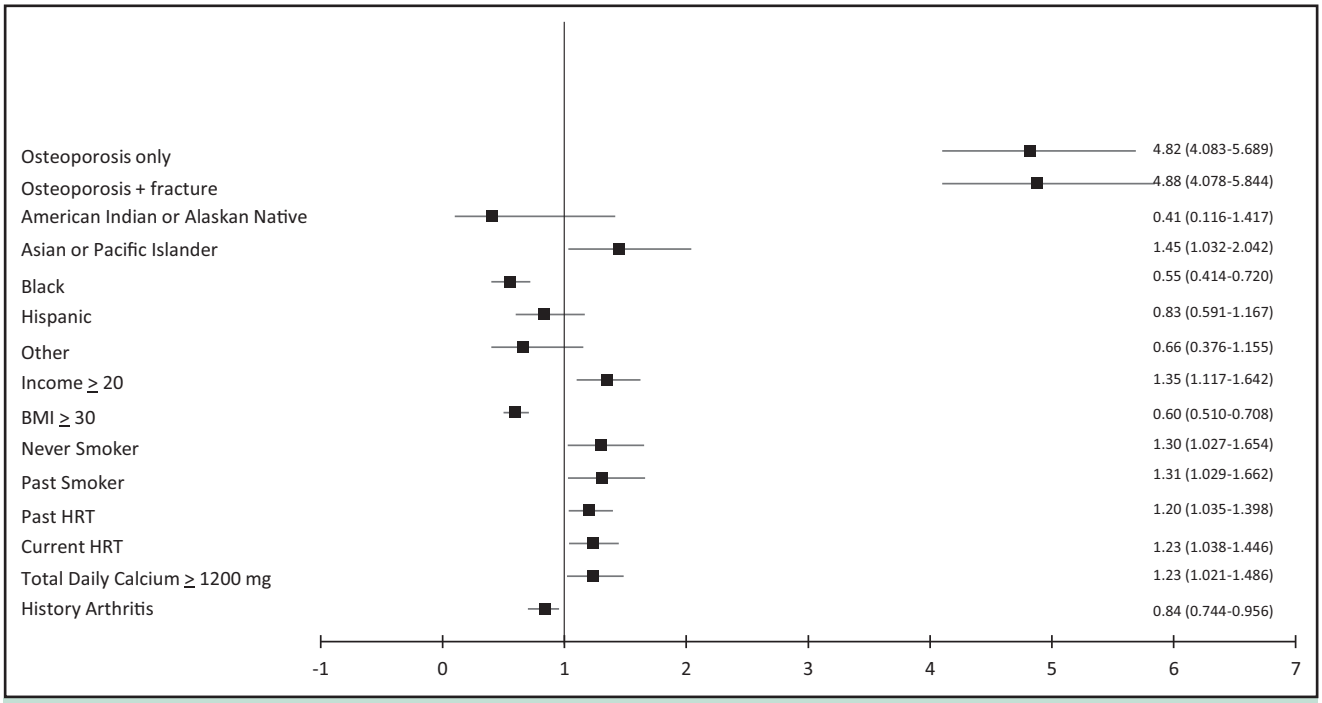

Figure 2 Odds ratios and 95% confidence intervals for appropriate osteoporosis treatment. Odds ratios have been adjusted for the following variables in the model: age, income, optimism, negative emotional construct, activities of daily living, alcohol intake, energy expenditures per week, vitamin D intake, calcium intake, education, number of medications, osteoporosis diagnosis by fracture site, race, region, smoking status, general health, insurance status, number of falls, health care provider, disability, marital status, mammograms, Pap smears, main job, depression, body mass index, self-rate health status, primary care provider visit in the past year, hormone use, number of medications, history of arthritis, cardiovascular disease, hypertension, hip replacement, and other joint replacement. HRT = hormone therapy.

reported the use of appropriate pharmacotherapy other than estrogen to reduce future fractures. Although some of these women may have had contraindications to treatment, this explanation is unlikely to account for the majority who were not on treatment after diagnosis of osteoporosis or fracture. Our findings can inform future studies as well as development of interventions and education programs aimed toward improving treatment of osteoporosis and prevention of fractures, as well as awareness about subgroups of older women particularly vulnerable to suboptimal osteoporosis treatment and fracture prevention. The potential translation to reduced morbidity and mortality has important public health relevance as the population ages, lives longer, and experiences greater cumulative exposure to factors detrimental to bone health.

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