Depressive Symptoms, Bone Loss, and Fractures in Postmenopausal Women

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BACKGROUND: Osteoporosis and depression may be associated through common physiologic systems or risk factors.

OBJECTIVE: To assess the associations between depressive symptoms (Burnam's scale) or antidepressant use and bone outcomes.

DESIGN: Prospective cohort study.

PARTICIPANTS: A total of 93,676 postmenopausal women (50 to 79 years old) enrolled in the Women's Health Initiative Observational Study.

MEASUREMENTS: Self-reported fractures ($n=14,982$) (hip [adjudicated], spine, wrist, and "other"). Analyses included 82,410 women with complete information followed on average for 7.4 years. Bone mineral density (BMD) of the hip ($n=4539$), spine ($n=4417$), and whole body ($n=4502$) was measured at baseline and 3 years in women enrolled at 3 densitometry study sites.

RESULTS: Overall, there were no statistically significant associations between depressive symptoms or antidepressant therapy and 3-year change in BMD. In a subset of women not using antidepressants, there was a significant difference in whole-body BMD change between women with and without depressive symptoms ($P=.05$). Depressive symptoms (hazard ratio [HR] 1.08; 95% CI=1.02 to 1.14) and antidepressant therapy (HR=1.22; CI=1.15 to 1.30) independently increased risk of any fracture, the majority of which occurred at "other" anatomic sites. Antidepressant therapy increased the risk of spine fracture (HR=1.36; CI=1.14 to 1.63). No associations were observed between depressive symptoms or antidepressant therapy and hip or wrist fracture.

CONCLUSION: In this study of postmenopausal women, average age 64, we observed minimal association between depressive symptoms and 3-year changes in either BMD or fracture risk. Antidepressant use was not

associated with changes in BMD, but was associated with increased risk of fractures at the spine and "other" anatomic sites.

KEY WORDS: depressive symptoms; antidepressants; bone density; fractures; prospective.

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INTRODUCTION

Osteoporosis and depression are common in women over age 50.^{1,2} Both conditions have multifaceted etiologies, but have physiologic processes in common that could provide biologic plausibility for an association. Corticosteroids, cytokines, and serotonin have been postulated to play a role in both depression³⁻⁶ and bone homeostasis.⁷⁻¹¹ Alternatively, the link could be caused by factors associated with depression that affect bone health such as inactivity, nutrition, weight, calcium intake, or smoking. Antidepressants may also have a direct effect on bone through serotonin pathways^{12,13} or have a complex relationship through falls or depressive symptomatology and severity.

Among the first epidemiological evaluations of depression and bone health was a small case-control study by Michelson and colleagues.¹⁴ They observed an association between clinically assessed depression and lower bone mineral density (BMD) and higher urinary cortisol excretion in premenopausal women. Prospective studies are limited. In postmenopausal women, 2 longitudinal studies have reported an association between depressive symptoms and hip BMD^{15,16} with 1 reporting no association at the spine.¹⁵ Longitudinal studies more consistently report a positive association between depressive symptoms and risk of nonvertebral or hip fractures.¹⁷⁻²⁰ Only 1 study examined other anatomic sites and reported an increase risk of spine but not wrist fracture after adjustment for antidepressant use.¹⁷

This prospective study investigates: (1) the association between self-reported depressive symptoms and bone health (3-year changes in BMD and fracture risk) at multiple anatomic locations in a large cohort of postmenopausal women

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while controlling for covariates known to influence bone outcomes, and (2) whether the use of antidepressants independently affects these associations.

METHODS

Participants

Participants were 93,676 postmenopausal women, aged 50 to 79 years, enrolled in the Women's Health Initiative (WHI) Observational Study (OS) between 1994 and 1998.²¹ Bone mineral density (BMD) measurements were collected on a subset of women ($n=6,441$) enrolled at the 3 designated bone densitometry clinics.²² Details have been previously described.²³⁻²⁶ Women were excluded if it was unlikely that they could participate for at least 3 years, including "serious emotional problems, mental illness, or too much stress, that would make it hard for women to be in a research study".²⁴ Therefore, women with more severe depression were likely excluded from the study. Human subjects review committees at each participating institution approved the study.²²

Exposure Measures

Depressive Symptoms. Baseline depressive symptoms were assessed by self-report using Burnam's 8-item scale for depressive disorders (major depression and dysthymia).²⁷ This scale combines 6 questions about frequency of depressive symptoms from the Center of Epidemiologic Studies Depression Scale (CES-D), with 2 questions about symptom duration from the Diagnostic Interview Schedule (DIS). The distribution of scores was highly skewed, suggesting a binomial distribution. Therefore, as has been done in other studies,²⁸ a cut point greater than or equal to 0.06 was used to dichotomize the continuous score.

Antidepressant Use. To measure antidepressant use, participants were asked to bring all current medications to baseline interviews.²⁹ Medication used for 2 or more weeks was recorded along with duration of use. We evaluated selective serotonin reuptake inhibitors (SSRIs) in subanalyses.

Outcome Measures

3-year Changes in Bone Mineral Density (BMD). Areal BMD measures (g/cm^2) were obtained at the hip, posterior-anterior lumbar spine (L2-L4 region), and the whole body at baseline and 3 years using dual-energy x-ray absorptiometry (DXA) Hologic QDR-2000 Series Bone Densitometers. Quality assurance was maintained through central review of scans, cross-calibration of scanners, and corrections for longitudinal changes.³⁰

Fracture. Any, hip (nonpathological), spine (thoracic or lumbar), wrist/lower arm (radius/ulna or 1 or more carpal bones) and "other" (tailbone, pelvis, femur shaft, knee, lower leg, ankle, foot, heel, clavicle, shoulder, upper arm, elbow, or hand [metacarpal]) inpatient and outpatient fractures were self-reported annually.³¹ As spine x-rays were not performed, morphometric vertebral fractures could not be assessed; only

clinically noted vertebral fractures are included. Hip fractures were centrally adjudicated by hospital record review. Traumatic fractures were not excluded.

Other Covariates

During the baseline visit, demographic data, reproductive and medical history, lifestyle, and behavioral factors were self-reported using standardized questionnaires.^{21,23} The physical function score (lowest function [0] to highest [100]) was calculated from the 10-item SF-36 physical functioning subscale.

Analysis

Distributions of participants' baseline characteristics were calculated in strata defined by depressive symptom status and use of antidepressant therapy.

BMD Change. Multivariable linear regression methods were used to assess the associations between 3-year changes in BMD and either depressive symptoms or antidepressant use. One model was developed for all anatomic sites. To identify confounding baseline variables, known determinants of BMD³² (Table 1) were included in models and variables that changed the point estimate by less than 10% were removed.³³ Using this process, the baseline variables of BMD, age (years), height (cm), weight (log kg), ethnicity (African-American, Latino, white, or other), physical function score, oral hormone therapy (opposed or unopposed; never, past, and current use), current smoking, and years since menopause were retained in the model. Owing to missing data on BMD, depression, and other variables, complete case analyses for hip, spine, and total body included 4,539, 4,417, and 4,502 participants, respectively.

Fracture. Semi-parametric Cox survival models were used to calculate hazard ratios for fracture occurrence. Length of follow-up (average 7.4 years) was calculated from day of enrollment to day of fracture, and observations were censored at the last follow-up visit or death ($n=5996$). The proportional hazards assumption was tested, and stratified estimates (stratum-specific baseline hazard with equal coefficients across strata) were calculated if needed. All analyses used multivariable models, developed as described above, and included baseline factors of age (years), height, weight (log kg); ethnicity (African-American, Latino, white, or other); years since menopause, physical function score, exercise, current smoking, ever having cardiovascular disease (CVD), analgesic/narcotic use, and history of previous fracture. After accounting for missing data and loss to follow-up ($n=507$), complete case analysis included 82,410 women.

Use of antidepressants can be a marker for more severe depressive symptoms or can reduce depressive symptoms and potentially obscure associations. To remove possible medication effects in our analyses of depressive symptoms, we performed subanalyses restricted to women not using antidepressants at baseline. Similarly, antidepressants are usually prescribed for depressive symptoms. To control for variability in bone outcomes that might be explained in part by depressive symptoms, we controlled for depressive symptoms in our

Table 1. Description of Baseline Characteristics of Participants by Depressive Symptoms* and Antidepressant Use

Characteristics	Depressive symptoms		Antidepressant use	
	No	Yes	No	Yes
	(n=80,755) [†]	(n=10,368) [†]	(n=86,463) [†]	(n=7,212) [†]
Depressive status				
Mean depressive symptom score (SD)	0.006 (0.01)	0.33 (0.25)	0.09 (0.30)	0.30 (0.46)
Percent antidepressant, current use	6	20	N/A	N/A
Percent SSRI, current use	3	12	N/A	49
Demographics				
Percent non-white [‡]	15	22	17	11
Mean age (SD)	64 (7)	62 (8)	64 (7)	62 (7)
Percent marriage-like relationship	63	51	62	59
Percent college graduate or above	44	33	43	41
Personal characteristics				
Percent non-drinkers (alcohol)	11	11	11	10
Percent current smokers	6	10	6	8
Mean physical function score [§] (SD)	82 (19)	72 (25)	82 (20)	71 (25)
Mean minutes of recreational activity/week (SD)	202 (186)	160 (174)	200 (187)	163 (173)
Mean height (cm) (SD)	162 (7)	161 (7)	162 (7)	162 (7)
Mean weight (kg) (SD)	71 (17)	75 (19)	71 (17)	76 (19)
Mean BMI	27 (6)	29 (7)	27 (6)	29 (6)
Medical and reproductive history				
Percent with history of personal fracture	38	40	38	44
Percent that fainted in last 12 months	2	5	2	4
Percent with no term pregnancy	13	12	13	14
Percent 5 or less years post menopause	15	18	16	16
Percent w/ prior bilateral oophorectomy	20	22	20	25
Percent ever having osteoarthritis	47	58	48	63
Percent ever having cancer	13	15	13	15
Percent ever having cardiovascular disease	18	24	19	24
Percent ever having diabetes	5	9	5	9
Percent ever having overactive thyroid	3	3	3	4
Medications and supplements				
Percent oral hormone therapy, current use	42	42	41	54
Mean calcium from supplements (mg/day) (SD)	403 (617)	346 (553)	392 (609)	423 (593)
Mean vitamin D supplementation (IU/day) (SD)	5 (6)	5 (7)	5 (6)	6 (6)
Percent oral contraceptives, ever use	40	44	39	47
Percent bisphosphonate, current use	2	2	2	2
Percent corticosteroid, current use	1	2	1	3
Percent analgesics or narcotics, current use	2	4	2	7
Percent thiazide, current use	5	6	5	7

*With depressive symptoms (Burnam ≥ 0.06) or without (Burnam score < 0.06)

[†]Totals number of participants described by depressive symptoms and antidepressant use are not equal because of missing data.

[‡]Participant described "most identified with" ethnic group (American Indian or Alaskan Native; Asian or Pacific Islander [ancestry is Chinese, Indo-Chinese, Korean, Japanese, Pacific Islander, Vietnamese, other]; Black or African American [not of Hispanic origin]; Hispanic/Latino [ancestry is Mexican, Cuban, Puerto Rican, Central American, or South American]; Other; White [not of Hispanic origin])

[§]The SF-36 quality of life subscale (lowest functioning [0]—highest functioning [100])

^{||}. Because of the large sample size and resulting statistical power the difference in characteristic distributions between exposed/non-exposed groups was statistically significant (p value $< .05$) except for these variables. Larger differences are highlighted under "Results". Model building is described in the "Analysis" section.

analyses of antidepressant use. As falls could be a mediating factor between depressive symptoms¹⁷ or antidepressant use³⁴ and fracture, we controlled for the number of falls (0, 1, 2, or 3+) in the year before baseline in a separate subanalysis. All analyses were performed using STATA version 9 software (College Station, TX, USA).

RESULTS

Participants

Full Cohort. Of the women in the full cohort ($n=93,676$), 11% ($n=10,368$) had depressive symptoms at enrollment (Burnam score ≥ 0.06); 8% ($n=7,212$) were using antidepressants and nearly half of these were using SSRIs (Table 1). On average, the women were 64 years old and 15 years beyond the age of

menopause. Compared to women without depressive symptoms, at baseline women with depressive symptoms were less likely to be married or living with a partner or to have graduated from college. They exercised less, took less calcium supplementation, had lower physical function, were more likely to be non-white, and were more likely to have arthritis or CVD. Compared to women not receiving antidepressant therapy, women using antidepressants on average had lower physical function, exercised less, and were more likely to be using hormone therapy.

BMD Subset. Of the women enrolled at the 3 BMD centers ($n=6,441$), 14% ($n=877$) had depressive symptoms, 8% ($n=508$) were receiving antidepressant therapy, and 3% were using SSRIs ($n=220$). Women in the BMD subset were similar to the full cohort in age, BMI, and physical function, but were less

likely to be white (77% vs 84%). Approximately 80% of the women had 3-year BMD measures. Women who were missing 3-year hip BMD measures had a higher probability of baseline depressive symptoms (mean Burnam score 0.07 vs 0.05).

BMD Change

Depressive Symptoms. Women with depressive symptoms had slightly higher average hip BMD measures at baseline (T score -0.78 versus -0.90) but similar spine (-0.64 vs -0.68) and whole body (-0.78 vs -0.83) BMD compared to those without depressive symptoms. We did not observe a statistically significant association between depressive symptoms and mean change in 3-year BMD at the hip or spine (Table 2). In women not using antidepressants, there was a minimal, but statistically significant 3-year difference in whole-body BMD change associated with depressive symptoms (-0.0036 g/cm²; $P=.05$).

Antidepressant Use. At baseline, women using antidepressants had higher mean BMD at the hip (T score -0.74 vs -0.90), spine (-0.38 vs -0.71), and whole body (-0.63 vs -0.85) compared to non-users. We did not observe any statistically significant associations between the use of antidepressants and 3-year changes in hip, spine, or whole-body BMD, after controlling for depressive symptoms and other potential confounding variables (Table 3).

Table 2. Adjusted* Difference in Average 3-year BMD Change (g/cm²) Between Women with and without Depressive Symptoms†

Anatomic site of BMD measure	Regression coefficient†,§ (95% CI) (referent group = women not using antidepressants)	P value
Hip		
Depressive symptoms*	.0015 (−.0015 to .0044)	.34
Depressive symptoms in women not using antidepressants*	.0015 (−.0018 to .0047)	.38
Spine		
Depressive symptoms*	−.0009 (−.0052 to .0035)	.69
Depressive symptoms in women not using antidepressants*	−.0004 (−.0052 to .0044)	.87
Whole Body		
Depressive symptoms*	−.0024 (−.0057 to .0008)	.14
Depressive symptoms in women not using antidepressants*	−.0036 (−.0070 to −.0001)	.05

*Adjusted for baseline BMD, age, years since menopause, ethnicity, physical function, height, log weight, oral hormone therapy, current smoking

†Depressive symptoms (Burnam score ≥ 0.06)

‡Regression coefficients show between group differences in average 3-year change in BMD (g/cm²). For example, at the hip, the mean change in BMD for women using versus not using antidepressants was within approximately 0.15% of each other over 3 years.

§Because of missing data on BMD (hip $n=1,295$; spine $n=1,591$; total body $n=1,338$), depression ($n=210$) and other variables, complete case analyses for the primary hip, spine, and total body models included 4,539, 4,417, and 4,502 participants, respectively. Models restricted to women not using antidepressants contained 4,177 (hip), 4,069 (spine), and 4,140 (whole body) observations.

Table 3. Adjusted* Difference in Average 3-year BMD Change (g/cm²) Between Women Using Versus not Using Antidepressants

Anatomic site of BMD measure	Regression coefficient†‡ (95% CI) (referent group = women not using antidepressants)	P value
Hip		
Antidepressant use*	.004 (.0002 to .0075)	0.04
Antidepressant use adjusted for depressive symptoms*§	.003 (−.0005 to .0069)	0.09
SSRI use adjusted for depressive symptoms*§	.001 (−.0044 to .0065)	0.70
Spine		
Antidepressant use*	.002 (−.0032 to .0074)	0.44
Antidepressant use adjusted for depressive symptoms*§	.002 (−.0031 to .0078)	0.40
SSRI use adjusted for depressive symptoms*§	−.003 (−.0105 to .0055)	0.54
Whole Body		
Antidepressant use*	.003 (−.0010 to .0070)	0.14
Antidepressant use adjusted for depressive symptoms*§	.003 (−.0007 to .0073)	0.10
SSRI use adjusted for depressive symptoms*§	.004 (−.0015 to .0102)	0.14

*Adjusted for baseline BMD, age, years since menopause, ethnicity, physical function, height, log weight, oral hormone therapy, current smoking

†Regression coefficients show estimated difference in average 3-year BMD change (g/cm²) between women using versus not using antidepressant after adjustment.

‡Complete case analysis included 4,614 (hip), 4,489 (spine), and 4,575 (whole body) participants; 4,539 (hip), 4,417 (spine), and 4,502 (whole body) after adjustment for depressive symptoms.

§Adjusted for depressive symptoms (Burnam score ≥ 0.06)

Fracture

During follow-up, women experienced 14,982 fractures: 1,132 (1%) hip fractures; 1,607 (2%) clinical vertebral fractures; 2,867 (3%) wrist fractures; and 11,128 (12%) fractures at “other” skeletal sites. The average time from enrollment to the first fracture occurrence was 4.4 years: hip 4.9 years, spine 5.2 years, wrist 4.7 years, and “other” locations 4.3 years.

Depressive Symptoms. There were no statistically significant differences in adjusted risk of hip, spine, or wrist fracture between women with and without depressive symptoms (Table 4). Depressive symptoms were associated with a minimal increased risk of any fracture (hazard ratio [HR] 1.08; 95% CI=1.02 to 1.14), the majority of which occurred at “other” anatomic sites (HR 1.16; 95% CI=1.09 to 1.23).

Antidepressant Use. We observed no association between antidepressant therapy and risk of hip or wrist fracture after controlling for depressive symptoms and other covariates (Table 5). Compared to women not using antidepressants, women using antidepressant medication had increased adjusted risk of any fracture (HR=1.22; 95% CI=1.15 to 1.30), clinical spine fracture (HR=1.36; 95% CI=1.14 to 1.63)

Table 4. Depressive Symptoms* and Adjusted† Hazard Ratios for Fracture

Anatomic site of fracture	Adjusted Hazard ratio† (95% CI)	P value
Any (13,129 fractures)		
Depressive symptoms	1.08 (1.02 to 1.14)	.006
Depressive symptoms in women not using antidepressants	1.04 (.97 to 1.10)	.25
Hip (914 fractures)		
Depressive symptoms	0.88 (0.70 to 1.10)	.26
Depressive symptoms in women not using antidepressants	0.87 (0.68 to 1.12)	.28
Clinical Spine (1,404 fractures)		
Depressive symptoms	1.05 (0.89 to 1.24)	.54
Depressive symptoms in women not using antidepressants	0.98 (0.80 to 1.19)	.86
Wrist (2,513 fractures)		
Depressive symptoms	0.98 (0.86 to 1.12)	.77
Depressive symptoms in women not using antidepressants	0.95 (0.82 to 1.10)	.48
Other Sites (10,156 fractures)		
Depressive symptoms	1.16 (1.09 to 1.23)	.000
Depressive symptoms in women not using antidepressants	1.11 (1.04 to 1.19)	.002

*Depressive symptoms (Burnam score ≥ 0.06) or without (Burnam score < 0.06)

†Adjusted for age, weight, height, ethnicity, years since menopause, physical function, exercise, current smoking, CVD, analgesic or narcotics, and previous fracture

‡Complete case analysis included 82,410 participants (82,374 for hip and any fracture owing to exclusion of 43 pathologic fractures); 76,037 when the analysis was restricted to women not using antidepressants.

and fractures at “other” locations (HR=1.24; 95% CI=1.15 to 1.32). Associations at these sites persisted, although the magnitude of the association decreased, after controlling for number of falls in the last 12 months (data not shown). This increase in risk was similar for women using antidepressants for less than or greater than 6 months at baseline. The risk estimates for SSRIs were similar in magnitude across anatomic sites although statistical significance was not achieved at the hip.

DISCUSSION

BMD Change

Depressive Symptoms. In this large prospective study, after adjusting for major covariates, we found no association between 3-year bone loss at the hip, spine, or whole body and self-reported depressive symptoms in our primary analyses. In a subanalysis of women not using antidepressants, we observed a slight difference in whole-body BMD change favoring women without depressive symptoms compared to those with symptoms.

To date, the evidence supporting an influence of depression on changes in BMD in postmenopausal women has not been uniformly strong. A few small cross-sectional and case-control studies reported an inverse association between clinically diagnosed depression and femoral or spinal BMD,^{14,35,36} whereas a larger cross-sectional study found no association.³⁷

A recent 1-year longitudinal study of 320 postmenopausal white women (average age 56 years) did not observe an

Table 5. Antidepressant Use and Adjusted Hazard Ratios for Fracture

Anatomic site of fracture	Adjusted Hazard ratio* (95% CI) (referent group = women not using antidepressants)	P value
Any		
Antidepressant use†	1.23 (1.16 to 1.30)	<.001
Antidepressant use adjusted for depressive symptoms†,‡	1.22 (1.15 to 1.30)	<.001
SSRI use adjusted for depressive symptoms†,‡	1.30 (1.20 to 1.41)	<.001
Duration of antidepressant use at baseline < 6 months†,‡	1.17 (1.02 to 1.34)	.02
Duration of antidepressant use at baseline ≥ 6 months†,‡	1.24 (1.16 to 1.32)	<.001
Hip		
Antidepressant use†	1.11 (0.88 to 1.40)	.39
Antidepressant use adjusted for depressive symptoms†,‡	1.14 (0.90 to 1.45)	.28
SSRI use adjusted for depressive symptoms†,‡	1.33 (0.95 to 1.86)	.10
Duration of antidepressant use at baseline < 6 months†,‡	1.49 (0.93 to 2.39)	.10
Duration of antidepressant use at baseline ≥ 6 months†,‡	1.07 (0.82 to 1.40)	.63
Clinical Spine		
Antidepressant use†	1.35 (1.14 to 1.61)	.001
Antidepressant use adjusted for depressive symptoms†,‡	1.36 (1.14 to 1.63)	.001
SSRI use adjusted for depressive symptoms†,‡	1.25 (0.96 to 1.63)	.09
Duration of antidepressant use at baseline < 6 months†,‡	1.40 (0.96 to 2.05)	.08
Duration of antidepressant use at baseline ≥ 6 months†,‡	1.36 (1.12 to 1.64)	.002
Wrist		
Antidepressant use†	1.14 (0.99 to 1.31)	.07
Antidepressant use adjusted for depressive symptoms†,‡	1.15 (0.99 to 1.33)	.06
SSRI use adjusted for depressive symptoms†,‡	1.29 (1.07 to 1.56)	.009
Duration of antidepressant use at baseline < 6 months†,‡	.91 (0.64 to 1.29)	.58
Duration of antidepressant use at baseline ≥ 6 months†,‡	1.20 (1.03 to 1.41)	.02
Other Sites		
Any antidepressant use†	1.25 (1.17 to 1.34)	<.001
Antidepressant use adjusted for depressive symptoms†,‡	1.24 (1.15 to 1.32)	<.001
SSRI use adjusted for depressive symptoms†,‡	1.32 (1.21 to 1.45)	<.001
Duration of antidepressant use at baseline < 6 months†,‡	1.21 (1.04 to 1.40)	.01

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Table 5. (continued)

Anatomic site of fracture	Adjusted Hazard ratio* (95% CI) (referent group = women not using antidepressants)	P value
Duration of antidepressant use at baseline ≥ 6 months ^{†,‡}	1.24 (1.15 to 1.34)	<.001

*Complete case analysis included 83,966 participants (83,927 for hip and any fracture because of exclusion of 43 pathologic fractures), and 82,410 in analyses that controlled for depressive symptoms.

†Adjusted for age, weight, height, ethnicity, years since menopause, physical function, exercise, current smoking, CVD, analgesic or narcotics, and previous fracture

‡Adjusted for depressive symptoms (Burnam score ≥ 0.06)

association between depressive symptoms and BMD loss at the more trabecular spine.¹⁵ A second study including older white women (average age 76, $n=4,177$) reported an inverse relationship between depressive symptoms and total hip BMD.¹⁶ Both studies reported an association between depressive symptoms and bone loss at the more cortical femoral neck region, but not at the trochanter. These studies are consistent with our findings in that we saw a decrease in whole-body BMD, a measure dominated by cortical bone. The disparity between the findings may partly be explained by differences in population ages, race, and the division of hip BMD by cortical and trabecular subregion.

Antidepressant Use. After controlling for depressive symptom status, we observed no association between antidepressant use and 3-year changes in BMD at the hip, spine, or in whole body. There is limited literature regarding the association between antidepressant therapy and BMD change. A recent cohort study followed 2,722 older women (average age 78.5; white only) for an average of 5 years and reported decreases in hip BMD associated with SSRI use, but not tricyclic antidepressants (TCAs), after controlling for depressive symptoms and in analyses that removed women with more severe depressive symptoms.³⁸ Rate of bone loss was not different in women who reported using antidepressants at only 1 versus both time points. The younger age of participants and shorter follow-up in our study could contribute to the difference in findings.

Fracture

Depressive Symptoms. We observed no increased risk of hip, wrist, or self-reported spine fractures associated with depressive symptoms in postmenopausal women. We did observe a slight increased risk of “any” fractures, most of which occurred at “other” skeletal sites. Two other studies, which did not adjust for antidepressant use, have reported elevated risk of hip fracture associated with only the highest level of depressive symptoms or mental distress.^{19,20} Another study has reported that mental distress, present at 2 different time periods, increased the odds of nonvertebral fractures; their sample size did not allow for stratification by use of “nerve” medicine.¹⁸ Similar to our results, Whooley et al. found an increased risk of self-reported, nontraumatic, nonvertebral fractures in older women ($n=7,414$) with depressive symptoms after adjusting for antidepressant use, along with no statistically significant associations for hip or

wrist fractures when assessed separately.¹⁷ In contrast to our findings, these authors observed higher odds of vertebral fracture in women. Their method for identifying spine fractures compared baseline and follow-up lateral radiographs. In our study, fractures were initially self-reported, which precluded assessment of morphometric spine fractures.

Antidepressant Use. We observed an association between antidepressant therapy and increased risk of any fracture, clinical spine fracture and fractures at “other” skeletal locations independent of depressive symptom status. Similarly, 2 other large cohort studies have reported an increase in nontraumatic, nonvertebral fractures associated with antidepressant³⁹ or SSRI⁴⁰ therapy.

In contrast to our findings, a number of case-control studies using automated data have reported increased risk of hip fracture with antidepressant use.^{41–46} This study design can be more vulnerable to bias owing to unmeasured covariates.⁴⁷ One cohort study has also reported a 65% increase risk of hip fracture with antidepressant therapy.³⁹ Compared to this study, our study analyzed a greater number of hip fractures (1,094 vs 288) and a larger percent of women received antidepressant therapy (8% vs 6%); this difference may be because of the younger average age of our study population (64 vs 77 years) or their exclusion of traumatic fractures.

The following points should be considered when interpreting the study results. Our study was well powered; we had 80% power to detect 3-year changes in hip and whole-body BMD of 0.008 g/cm² and a 0.01 g/cm² change at the spine. However, certain characteristics inherent to our study could partially explain our null BMD findings. The women in our study were heavy (mean BMI 27 kg/m²; SD 5.9) and a disproportionate number of minority women were recruited at the densitometry sites. In addition, the WHI exclusion criteria included serious emotional problems and mental illness so it is likely the women in our study had fewer depressive symptoms than the general population. However, the range in the Burnam depressive symptom score appeared adequate (0.00 to 0.96) to provide variability. We also used a measure of self-reported depressive symptoms, not a clinical diagnosis of depression. An ancillary study assessed the reliability of the Burnam instrument in a subset of WHI OS volunteers and reported 74% sensitivity and 87% specificity among women with DSM-IV defined current major depression and dysthymia.²⁸ Such measurement error could bias our results toward the null. However, another study of younger women with low levels of depressive symptoms excluded women with low BMD and still reported an association between femoral neck BMD and Beck Depression Inventory score (BDI).¹⁵ These authors repeated their analysis replacing the BDI with the Burnam measure and found persistence of the association with changes in femoral neck BMD ($p=0.09$). Finally, depression may be associated with study withdrawal or with incomplete information. We did observe higher baseline depressive scores in women with incomplete BMD data.

Our hip fractures were centrally adjudicated; however, all other types of fractures were self-reported so morphometric vertebral fractures could not be assessed. Local adjudication of a sample of self-reported WHI fractures confirmed 80% of other fractures ($n=3,011$), but only 52% of spine ($n=302$) fractures.^{25,31} Vertebral fractures are also reported to be under-

diagnosed.^{48,49} This misclassification, if nondifferential, could have reduced the magnitude of the association seen in our study at this anatomic site. Alternatively, depression has been associated with illness behavior and increased utilization of health services, which could result in differential higher reporting in this group, potentially increasing ascertainment and the magnitude of association.⁵⁰⁻⁵³

As this is an observational study, although we adjusted for numerous covariates, there is always the potential for residual confounding as a result of imperfect measurement of variables or unmeasured covariates, especially in the area of confounding by indication of antidepressant use. We also used baseline exposure data, which does not account for depressive symptoms or antidepressant use after baseline.

CONCLUSION

Osteoporosis and resultant fractures are a growing public health concern. This sizable study adds to the body of knowledge regarding a common exposure, depression, and its influence on bone at a potentially vulnerable phase of life when the trajectory of bone metabolism is trending down. Thus, it is reassuring to observe minimal association of depressive symptoms or antidepressant therapy on 3-year changes in BMD in this group of generally healthy postmenopausal women. Our findings also provide additional evidence for an association between antidepressant medication and increased risk of fracture at some skeletal sites. Future randomized controlled trials of antidepressants should evaluate fractures as an outcome.

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