Rates of Bone Loss Among Women Initiating Antidepressant Medication Use in Midlife

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Context: Concern has been raised that medications that block serotonin reuptake may affect bone metabolism, resulting in bone loss.

Objective: The aim of the study was to compare annual bone mineral density (BMD) changes among new users of selective serotonin reuptake inhibitors (SSRIs), new users of tricyclic antidepressants (TCAs), and nonusers of antidepressant medications.

Design and Setting: We conducted a prospective cohort study at five clinical centers in the United States.

Participants: The study included 1972 community-dwelling women, aged 42 years and older, enrolled in the Study of Women's Health Across the Nation (SWAN).

Exposure: The use of antidepressant medications was assessed by interview and verified from medication containers at annual visits. Subjects were categorized as nonusers (no SSRI or TCA use at any examination), SSRI users (initiated SSRI use after the baseline SWAN visit), or TCA users (initiated TCA use after the baseline visit), using a computerized dictionary to categorize type of medication.

Main Outcome Measures: BMD at the lumbar spine, total hip, and femoral neck was measured using dual-energy x-ray absorptiometry at annual visits.

Results: BMD was compared among 311 new users of SSRIs, 71 new users of TCAs, and 1590 nonusers. After adjustment for potential confounders, including age, race, body mass index, menopausal status, and hormone therapy use, mean lumbar spine BMD decreased on average 0.68% per year in nonusers, 0.63% per year in SSRI users ($P = .37$ for comparison to nonusers), and 0.40% per year in TCA users ($P = .16$ for comparison to nonusers). At the total hip and femoral neck, there was also no evidence that SSRI or TCA users had an increased rate of bone loss compared with nonusers. Results were similar in subgroups of women stratified by the Center for Epidemiologic Studies Depression Scale (<16 vs ≥ 16).

Conclusions: In this cohort of middle-aged women, use of SSRIs and TCAs was not associated with an increased rate of bone loss at the spine, total hip, or femoral neck. **(*J Clin Endocrinol Metab* 98: 4355–4363, 2013)**

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Abbreviations: BMD, bone mineral density; BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; DXA, dual-energy x-ray absorptiometry; MAO-I, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine inhibitor; SSRI, selective serotonin reuptake inhibitor; SWAN, Study of Women's Health Across the Nation; TCA, tricyclic antidepressant.

Antidepressants are one of the most commonly prescribed classes of medications in the United States, used by approximately 1 in 10 Americans (1). Two-thirds of these prescriptions are for selective serotonin reuptake inhibitors (SSRIs) (2), which inhibit the serotonin transporter. The identification of serotonin receptors and functional serotonin transporters in osteoblasts, osteocytes, and osteoclasts (3–8) has suggested a role for serotonin in the regulation of bone metabolism and raised the possibility that SSRIs may have an effect on bone health (9, 10).

Considerable uncertainty remains about the role of serotonin in regulating bone metabolism. Animal studies of a role for serotonin in bone metabolism and of an effect of serotonin transporter inhibition have yielded mixed results, with some studies suggesting that serotonin and serotonin transporter inhibition may have a negative effect on bone health (11–13) and others suggesting a possible beneficial effect (6, 14–16). In humans, most studies examining a possible relationship between SSRI use and bone mineral density (BMD) have been cross-sectional (17–21) and have examined relatively homogeneous populations with respect to race and ethnicity. The few longitudinal prospective studies have been conducted in samples of older persons, limiting generalizability (22, 23), and have reported conflicting results; no prospective work has examined women in midlife.

Understanding the potential effects of SSRIs on BMD in women in perimenopause and early postmenopause, when bone loss accelerates, is of particular importance, given their widespread use in this age group. Over 22% of women between the ages of 40 and 59 in the United States were treated with these agents between 2005 and 2008 (2), the highest usage rate of any age group in either gender.

To determine whether SSRI use among women in midlife is associated with increased rates of bone loss, we used data from the Study of Women's Health Across the Nation (SWAN), a prospective cohort study of women transitioning through the menopause. Data available in the SWAN cohort include medication inventories at each annual visit, validated measures of depressive symptoms, detailed data on menopausal status, comprehensive assessment of other risk factors for osteoporosis and fractures, and in most women, annual measures of BMD at multiple skeletal sites. We also examined whether the use of tricyclic antidepressants (TCAs), an older class of antidepressants that inhibit uptake of serotonin to varying degrees, was associated with increased rates of bone loss in this cohort.

Subjects and Methods

Study design

We compared the rate of change in BMD among individuals who initiated SSRI use, individuals who initiated TCA use, and individuals who did not initiate use of either class of medication during the period from the baseline SWAN visit to the 10th annual visit (visit 10). This approach, known as a new-user design, has several advantages over analyses examining prevalent medication users (24). Analyses comparing prevalent medication users to nonusers may undersample short-term users of the medication and result in underascertainment of outcomes that occur early in the use of the medication. Individuals who have been using medication for a longer time (and are probably less likely to have suffered secondary or adverse effects) are oversampled. In addition, analyses examining prevalent medication use are limited in their ability to control for disease risk factors that may be altered by the medications under study (24). For the present analysis, depression, a potential risk factor for bone loss, may be altered by the use of SSRIs or TCAs.

Study population

SWAN is a multisite, longitudinal, community-based cohort study of 3302 women who were 42–52 years old at study entry (1996–97) and either premenopausal (no change in regularity of menses in past 12 mo) or early perimenopausal (change in regularity of menses in past 12 mo but menstruated in past 3 mo). Participants had to have an intact uterus and at least one ovary and not be using estrogen or other medications known to affect ovarian function. Participants were recruited at seven study sites. All sites recruited Caucasians, and each site enrolled women belonging to a prespecified minority ethnic group: African Americans in Pittsburgh, Boston, Detroit, and Chicago; Japanese and Japanese Americans in Los Angeles; Chinese and Chinese Americans in Oakland, California; and Hispanics in Hudson County, New Jersey. Details about the design and recruitment for SWAN are available (25). BMD was measured annually for SWAN participants at five of the seven sites. Chicago and New Jersey sites did not measure BMD.

To identify new users of a SSRI or TCA, we first excluded participants who reported use of either class of medication at the first SWAN visit to eliminate prevalent users at the start of the study. Participants who reported SSRI or TCA use at a subsequent visit were identified as new SSRI or TCA users. For the SSRI and TCA users, we considered study baseline to be the visit prior to the first time subjects reported new use of these medications. For participants not reporting use of these medications, we randomly selected a frequency-matched baseline visit to establish a comparable baseline (see Appendix A, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

To be included in the analysis, participants had to have a baseline BMD measurement and at least one additional BMD. Users of a serotonin-norepinephrine inhibitor (SNRI) or monoamine oxidase inhibitor (MAO-I) were excluded, as were pregnant women (Figure 1). Subjects who reported the use of both an SSRI and a TCA, who switched between the two classes of medications, or who initiated use of a SNRI or MAO-I at a later visit were censored at that visit.

Signed, written consent was obtained from all study participants at the screening. The informed consent procedures, study protocol, and forms were approved by all SWAN site Institutional Review Boards.

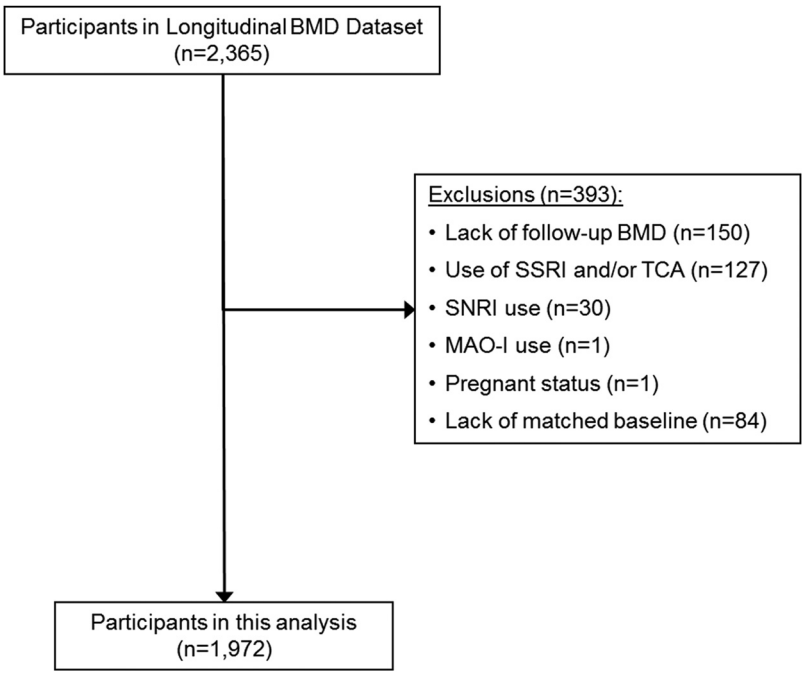

Figure 1. Study cohort.

Ascertainment of antidepressant medication use

At each annual visit, interviewer-administered questionnaires were used to ascertain all medication use since the last study visit. Use was verified by inspection of medication containers. The type of medication was classified from product brand or generic names using a computerized medication dictionary (Iowa Drug Information Service Drug Vocabulary, College of Pharmacy, University of Iowa).

Measurement of BMD

BMD of the lumbar spine, femoral neck, and total hip (g/cm^2) was measured by dual-energy x-ray absorptiometry (DXA) using Hologic instruments (Hologic Inc.). Three sites used Hologic 4500A models throughout. Two sites upgraded from 2000 to 4500A models at visit 8. These sites scanned 40 women on both their old and new machines to develop cross-calibration regression equations. As part of standard quality control measures, each DXA laboratory measured a Hologic anthropomorphic spine phantom once daily and a Hologic anthropomorphic spine phantom that was circulated to each laboratory for cross-calibration. Measurements of the local spine phantom and the circulating spine phantoms were analyzed by Synarc, Inc, and used by the study's coordinating center to adjust DXA measurements for minor temporal or geographic variations in densitometer performance. Additional quality control measures included review of every scan image by a local site investigator and review by Synarc, Inc, of 5% of all scans and all problem scans (26, 27). Short-term in vivo measurement variability was 0.014 g/cm^2 (1.4%) for the lumbar spine and 0.016 g/cm^2 (2.2%) for the femoral neck.

Measurement of depressive symptoms

Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D), a self-report questionnaire of 20 questions used to screen for depression (range of scores, 0–60). A cutoff of 16 or higher was used to define the presence of potentially clinically significant depression (28, 29); this cutoff has an average sensitivity for identifying depression of 84% and specificity of 74% (30).

Other measurements

At each annual visit, participants underwent measurement of height and weight for calculation of body mass index (BMI; weight in kilograms divided by the square of height in meters) and completed standard interviewer-administered or self-administered questionnaires that assessed demographic characteristics (age, ethnicity, income, marital status, education), lifestyle factors (smoking status, alcohol intake), hormone use, self-assessed health status, social support (4 items from the 20-item Medical Outcomes Study Social Support Survey) (31), medication use, vasomotor symptoms, and comorbid conditions. Physical activity was measured using a modified version of the Baecke Physical Activity Questionnaire (range, 3–15) (32, 33). Because physical activity was not measured at every visit, the missing visits were interpolated (see Supplemental Data, Appendix B).

Menopause transition stage was assessed annually in SWAN based on bleeding criteria. Categories were: premenopause (no decreased regularity in menstrual bleeding during the last year), early perimenopause (decreased menstrual regularity in the past year and menstrual bleeding in the past 3 mo), late perimenopause (no menses for 3–11 mo), and postmenopause (no menses for 12 or more months). Women reporting hysterectomy or oophorectomy were classified as surgically menopausal.

Statistical analysis

Descriptive statistics (mean, median, and range) of the baseline demographic variables, depression scores, physical activity, and BMI were calculated. Continuous variables were analyzed using ANOVA and Kruskal-Wallis tests, whereas categorical variables were analyzed using χ^2. Variables were transformed where necessary.

For the primary outcome, annualized change in BMD, we normalized the rate of change in BMD to the baseline BMD and obtained an annual percentage change in BMD for each woman. This approach provides easily clinically interpretable results and allows comparison of our results to other studies.

All analyses used a mixed-effects regression modeling strategy, allowing for a random intercept and slope (34). The annualized change in BMD was defined at each visit included in the analyses, rather than computing a woman-specific slope based on all of a subject's observations. Factors selected a priori for inclusion in the base models included years from the baseline visit as a continuous linear covariate and several covariates known to be possible correlates of BMD: study site, race/ethnicity (Caucasian, African American, Chinese, Japanese), age, and BMI (time-varying). Menopause transition stage (time-varying) was also included in all models.

Other covariates of interest that we tested for inclusion in multivariable models were baseline CES-D, calcium supplement use (yes/no), vitamin D supplement use (yes/no), current smoking (yes/no), self-reported health status (excellent/good, fair, poor/very poor), alcohol use (none, < once a month; moderate, > once a month; high, ≥ two times a week), annual income level, educational attainment, marital status, social support (continuous; range, 0–16), vasomotor symptoms (yes/no), and physical activity (continuous; range, 3–14). Time-varying covariates examined for inclusion in the models included selected medication use (bisphosphonates, hormone therapy, oral glucocorticoids, and thiazide diuretics) and selected comorbid conditions (osteoporosis, thyroid disease, cancer, diabetes mellitus). Only those covariates with P values <.10 were entered into the models with the a priori variables. Final models included only those covariates with P values <.05. Interactions between antidepressant use and menopausal transition stage were explored, as were interactions between antidepressant use and hormone therapy. Two-tailed P values <.05 were considered statistically significant for main and interaction effects.

Because depressive symptoms have been associated with higher rates of bone loss in some studies (35–37), we performed secondary analyses in which we stratified by CES-D <16 vs ≥16. In addition, we performed analyses in which subjects were censored when they reported hormone, steroid, bisphosphonate, or thiazide use.

SAS version 9.2 (SAS Institute, Inc) was used for the analyses.

Results

Characteristics of the study sample

Of the 2365 women in the SWAN longitudinal BMD data set, 150 were excluded for lack of a follow-up BMD, and 119 were excluded because they reported use of a SSRI or TCA at the initial SWAN visit. An additional 8 were excluded for use of a SSRI and TCA, 30 for use of a SNRI, and 1 for use of a MAO-I. One participant was excluded due to pregnant status (Figure 1). Eighty-four nonusers could not be matched to the users' baseline visit distribution and were also excluded from the analysis (Figure 1) for a final analytic cohort of 1972.

Of the 1972 women eligible for the analysis, 311 (15.8%) initiated SSRI use during the follow-up period, and 71 (3.6%) initiated TCA use. The remaining 1590 women reported no use of a SSRI or TCA at any visit. On average, women in the study cohort had 6.3 (±2.8) DXA exams and were followed for 5.9 (±2.9) years. Specific drug use among women taking SSRIs and TCAs is shown in Table 1.

Baseline characteristics of the cohort by antidepressant status are shown in Table 2. Participants reporting new use of a SSRI were more likely to be Caucasian, have a higher BMI, smoke tobacco, report use of hormone therapy, and have a higher CES-D score than TCA users or nonusers. TCA users were more likely to report poor or fair health status.

Table 1. SSRIs and TCAs Initiated During SWAN

SSRIs	311 (100)
Fluoxetine	85 (27.3)
Paroxetine	73 (23.5)
Sertraline	75 (24.1)
Citalopram	57 (18.3)
Escitalopram	18 (5.8)
Fluvoxamine	3 (1.0)
TCAs	71 (100)
Amitriptyline	36 (50.7)
Nortriptyline	21 (29.6)
Imipramine	1 (1.4)
Desipramine	1 (1.4)
Doxepin	9 (12.7)
Clomipramine	1 (1.4)
Mirtazapine	2 (2.8)

Data are expressed as number (percentage).

Rate of change in BMD by SSRI and TCA use status

In a base model controlling for age, menopausal status, site, race, and BMI, women taking SSRIs did not experience a higher annualized rate of bone loss at the spine or femoral neck than women not reporting use of a SSRI or TCA (nonuse) (spine, −0.67% vs −0.72%, $P = .36$; femoral neck, −0.70% vs −0.75%, $P = .49$) (Figure 2A). At the total hip, SSRI users had a lower mean annualized rate of bone loss compared to nonusers (−0.35% vs −0.47%; $P = .005$). Addition of the baseline CES-D score to the base models did not change the results, nor did addition of the presence of vasomotor symptoms. In final multivariable models, results were also similar, although the difference in the rate of bone loss between SSRI users and nonusers at the total hip was no longer significant (Figure 2B).

There was also no evidence that women reporting use of a TCA experienced higher annualized rates of bone loss compared to nonusers. In a base model controlling for age, menopausal status, site, race, and BMI, women taking TCAs experienced a −0.35%/year rate of bone loss at the spine, compared to −0.72%/year for women on no antidepressant medications ($P = .10$); at the femoral neck and total hip, women reporting use of a TCA also experienced on average a lower annualized rate of bone loss than nonusers, although none of the results reached statistical significance (Figure 2A). Results were similar with the addition of the baseline CES-D score to the base model and in the final multivariable models (Figure 2B).

In secondary analyses, we censored women when they reported use of hormone therapy, bisphosphonates, thiazide diuretics, or oral glucocorticoids. Although the point estimates of the mean annualized rates of bone loss did differ by exposure group in these secondary analyses compared to the primary analyses, the conclusions remained

Table 2. Characteristics by Category of Antidepressant Use

Characteristic	Nonusers	TCA Users	SSRI Users	*P* Value
n	1590	71	311	
Age, mean (SD), y	49.7 (3.9)	49.7 (4.5)	49.6 (3.7)	.94
Site, n (%)[a]				<.0001
Michigan	300 (18.9)	18 (25.4)	95 (30.2)	
MGH	289 (18.2)	10 (14.1)	67 (21.5)	
UCDavis	343 (21.6)	17 (23.9)	37 (11.9)	
UCLA	378 (23.8)	14 (19.7)	42 (13.5)	
Pittsburgh	280 (17.6)	12 (16.9)	70 (22.5)	
Ethnicity, n (%)				<.0001
Caucasian	738 (46.4)	40 (56.3)	196 (63.0)	
Black	306 (25.5)	18 (25.4)	96 (30.9)	
Chinese	207 (13.0)	8 (11.3)	9 (2.9)	
Japanese	239 (15.0)	5 (7.0)	10 (3.2)	
Menopausal status, n (%)				.09
Surgical menopause	44 (2.8)	5 (7.0)	12 (3.9)	
Postmenopausal	388 (24.5)	13 (18.3)	75 (24.1)	
Late perimenopausal	55 (3.5)	1 (1.4)	14 (4.5)	
Early perimenopausal	687 (43.3)	32 (45.1)	129 (41.5)	
Premenopausal	309 (19.5)	17 (23.9)	49 (15.8)	
Unknown	102 (6.4)	3 (4.2)	32 (10.3)	
BMI, mean (SD), kg/m^2	27.7 (6.8)	28.8 (7.5)	29.9 (7.6)	<.0001
CES-D score (scale 0–58), mean	8.4	8.8	13.9	<.0001
CES-D score ≥16, n (%)	258 (16.4)	15 (21.1)	115 (37.7)	<.0001
Self-reported health status, n (%)				.0002
Excellent or good	1386 (87.8)	56 (80.0)	258 (84.0)	
Fair	179 (11.3)	11 (15.7)	37 (12.1)	
Poor or very poor	14 (0.9)	3 (4.3)	12 (3.9)	
Current smoker, n (%)	197 (12.4)	4 (5.6)	60 (19.4)	.002
Current calcium supplement user, n (%)	935 (78.4))	47 (82.5)	174 (80.1)	.6
Current vitamin D supplement user, n (%)	917 (76.9)	45 (78.9)	170 (78.7)	.8
Alcohol intake				.04
High use (≥2 times/wk)	339 (21.3)	12 (16.9)	82 (26.4)	
Baecke physical activity score, mean (SD)[b]	7.8 (1.36)	7.5 (1.6)	7.5 (1.4)	.006
Lumbar spine BMD, mean (SD), g/cm^2	1.05 (0.15)	1.06 (0.15)	1.07 (0.16)	.07
Femoral neck BMD, mean (SD), g/cm^2	0.82 (0.13)	0.83 (0.13)	0.86 (0.14)	.0002
Total hip BMD, mean (SD), g/cm^2	0.94 (0.14)	0.95 (0.14)	0.99 (0.15)	<.0001
Vasomotor symptoms, n (%)	727 (45.9)	40 (56.3)	169 (54.9)	.005
Comorbidities, n (%)				
Thyroid disease (over-/underactive)	144 (9.1)	8 (11.4)	36 (11.6)	.50
Cancer	16 (1.0)	1 (1.4)	10 (3.3)	.009
Diabetes	90 (5.7)	6 (8.5)	31 (10.0)	.01
Osteoporosis	22 (1.4)	5 (7.1)	8 (2.6)	.01
Medication use, n (%)				
Hormone therapy	184 (11.6)	6 (8.6)	55 (17.7)	.007
Biphosphonate	16 (1.0)	3 (4.2)	8 (2.6)	.01
Oral glucocorticoid	116 (7.3)	6 (8.4)	41 (13.2)	.003
Thiazide	121 (7.6)	6 (8.5)	38 (12.2)	.03

[a] Sites: Michigan—University of Michigan, Ann Arbor, Michigan; MGH—Massachusetts General Hospital, Boston, Massachusetts; UCDavis—University of California, Davis, California; UCLA—University of California, Los Angeles, California; Pittsburgh—University of Pittsburgh, Pittsburgh, Pennsylvania.

[b] Modified version of Baecke with the imputed values for the visits not collected.

the same: there was no evidence of a greater rate of bone loss at the spine, femoral neck, or total hip among SSRI users or TCA users compared to nonusers. Results of these secondary analyses are illustrated in Figure 3, A (base models) and B (final multivariable models).

There was evidence of an interaction between antidepressant use and menopausal stage, with TCA users having a lower mean BMD at the spine when initiating treatment in premenopause compared to nonusers ($P = .02$). There was also evidence of an interaction between hormone therapy use and antidepressant medication use such that women using both hormone therapy and TCAs or SSRIs had lower BMD ($P = .01$ and $P = .03$, respectively).

In secondary analyses stratified on CES-D score (<16 vs ≥16), results were similar to the primary analyses: there was no evidence of higher rates of bone loss for SSRI users or TCA users in these subgroups.

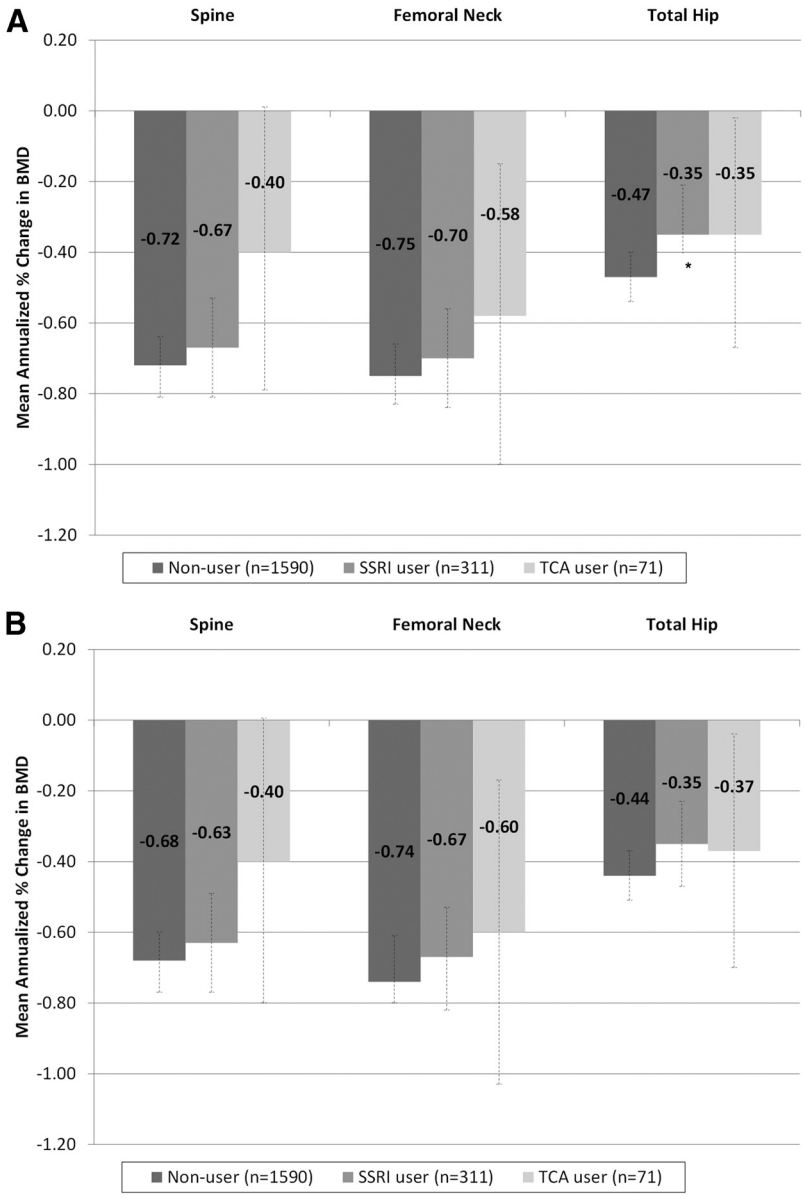

Figure 2. Mean annualized change in BMD by category of antidepressant use. A, Base model at all sites adjusted for age, site, menopausal status, race, and BMI. B, Multivariable model at each site. Spine: Base model + HT, physical activity, osteoporosis, thiazide use, menopausal stage*category of antidepressant use, HT*category of antidepressant use. Femoral neck: Base model + HT, osteoporosis, thiazide use, menopausal stage*category of antidepressant use. Total hip: Base model + HT, osteoporosis, thiazide use, menopausal stage*category of antidepressant use, diabetes, CES-D. *, $P = .005$ for comparison between SSRI users and non-users. HT, hormone therapy use.

Discussion

We found no evidence that use of SSRIs or TCAs among women in midlife was associated with an increased rate of bone loss. This finding was consistent at three skeletal sites (lumbar spine, total hip, and femoral neck) and did not differ by level of depressive symptoms.

Previous work has suggested a possible adverse effect of SSRIs on BMD (9, 17, 19–22), leading to calls for the identification of SSRI use as a risk factor for osteoporosis and for increased BMD screening in SSRI users (38, 39). However, much of the work in humans examining antidepressant use and BMD has had significant limitations, including cross-sectional designs and a limited ability to measure important confounders (17, 19–21, 40). Of the two published longitudinal studies of BMD change among SSRI users, the one that was focused on an elderly population (mean age, 80 y) found an association between SSRI use and increased bone loss (22). The other, using data from the Women's Health Initiative, did not observe an association between SSRI use and rate of change in BMD (23).

The present analysis has several advantages over these previous reports. In this prospective cohort study with yearly visits, we were able to use annual BMD measurements, update medication use status annually, and update other important covariates such as menopausal status annually. The previous longitudinal analyses measured only two time points, separated 3–5 years apart, and were unable to ascertain medication use in the intervening years. In addition, we examined new users of these medications, rather than prevalent medication users, as the other two prospective studies did. This new-user design addresses possible confounding introduced by including prevalent antidepressant users: prevalent users at the initial SWAN visit may have been on these medications for a long period of time, suggesting that they may have more severe depression, a potential confounder because depression itself may be a risk factor for accelerated bone loss (35–37, 41–43). Alternatively, depression may be altered by the use of SSRIs or TCAs. With the new-user design, measurement of this important potential confounder can occur before the initiation of the medication rather than after, as is the case when prevalent users are included in the analysis.

Even with the use of the new-user design, confounding by indication remains an important potential source of bias in observational studies examining the association

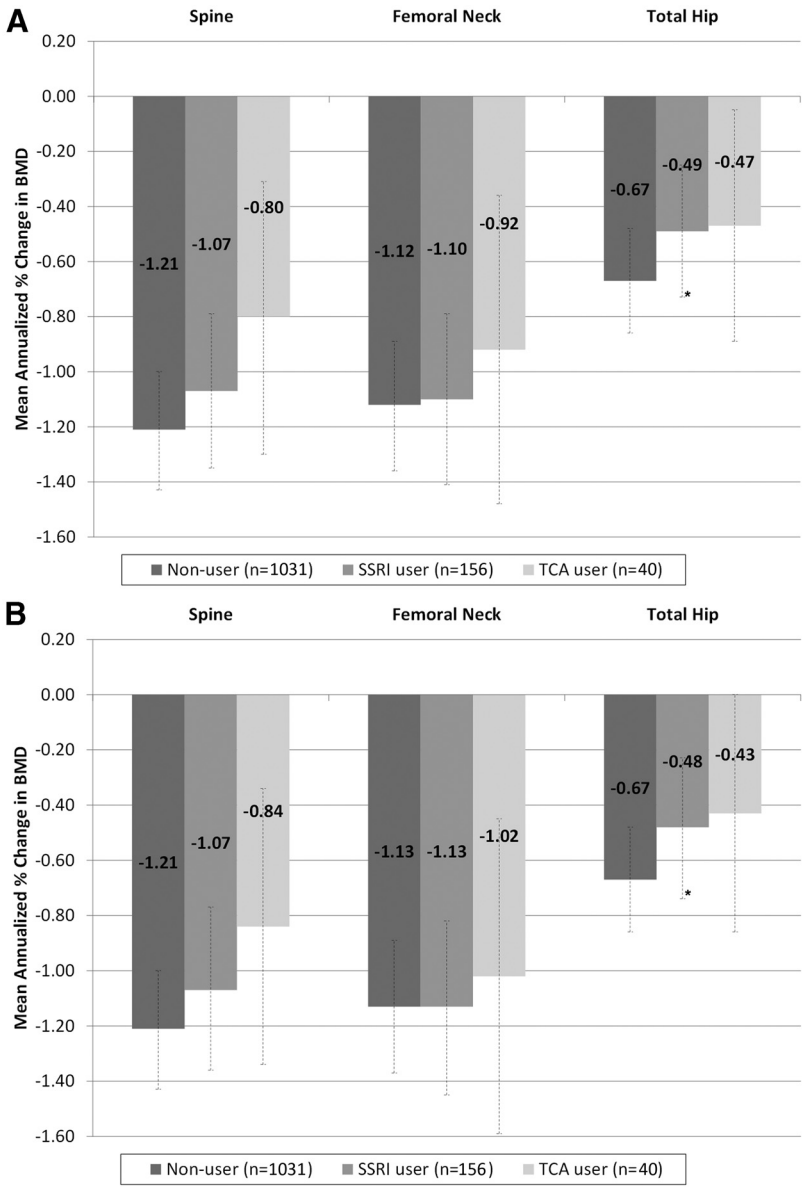

Figure 3. Mean annualized change in BMD by category of antidepressant use in cohort censoring users of bone active medications. A, Base model at all sites adjusted for age, site, menopausal status, race, and BMI, censored for use of bone active medications. B, Multivariable model at each site, censored for use of bone active medications. Spine: Base model +, physical activity, osteoporosis, menopausal stage*category of antidepressant use. Femoral neck: Base model + osteoporosis, menopausal stage*category of antidepressant use. Total hip: Base model + menopausal stage*category of antidepressant use, diabetes, CES-D. *, $P = .03$ for comparison between SSRI users and nonusers.

between antidepressant use and bone outcomes because antidepressants are often prescribed for depressive symptoms and depressive symptoms have been linked to lower BMD, higher rates of bone loss, and higher risk of fracture (35–37, 42–45). To further address this concern, we performed analyses controlling for CES-D score and stratifying on CES-D category (<16 vs ≥16) and observed no evidence that SSRI use was associated with higher rates of bone loss than nonusers.

A large body of work has reported associations between antidepressant use and fracture risk (20, 23, 46–51), an outcome not assessed in the present analysis. Our findings suggest that if antidepressant use is associated with an increased fracture risk, the mechanism of that association is not due to effects of the medications on BMD. Instead, mechanisms such as an increased risk of falls in antidepressant users (45) may explain those findings. Alternatively, the observed association between antidepressant use and fracture risk may be due to unmeasured confounding because antidepressant use may be a marker for other conditions associated with fracture risk, such as depression, comorbid conditions, and poor health status (52). Many of the studies examining antidepressant use and fracture risk have used administrative databases, which have significant limitations in their ability to control for many important potential confounders, such as BMD, BMI, depressive symptoms, and frailty. In the present study, we were not able to examine fracture risk, due to the low number of fractures in this healthy, middle-aged cohort.

Although our analysis has many advantages over existing work, there remain significant limitations. These results, which differ from those found in a cohort of elderly women (mean age, 80 y) (22), may not be generalizable to populations other than women in midlife. In addition, we did not have information about past use of SSRIs and TCAs, and we had limited information on medication use that occurred between the annual visits. Cohorts linked to pharmacy databases, allowing more comprehensive evaluation of duration and dose of therapy, would be optimal populations to further investigate the relationships between antidepressant use and bone outcomes.

To our knowledge, no randomized controlled trial of antidepressants has included measurement of BMD, fracture ascertainment, or measurement of other bone parameters as outcomes. Although a randomized, placebo-controlled trial would be the ideal, "gold standard" approach

to determining whether use of SSRIs or TCAs has a clinically significant effect on bone outcomes, such a trial is likely not feasible, given ethical concerns and the long follow-up time required to observe differences in fracture risk and change in BMD. As a result, analyses of observational cohorts are likely to represent our best opportunity to explore these potential associations, and SWAN offers a unique opportunity to do so in a cohort of middle-aged women.

Our findings should provide reassurance for women in midlife regarding the effects of SSRIs and TCAs on bone loss during the menopausal transition. Although initiating pharmacological therapy always requires careful balance of potential risks and benefits of the treatment, these results suggest that SSRIs and TCAs do not appear to have adverse effects on BMD in women in this age group.

SWAN Clinical Centers

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K.R. performed the statistical analyses and is independent of any commercial funder. She had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

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