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ORIGINAL RESEARCH

Use of Antidepressant Medications and Risk of Fracture in Older Women

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Abstract Use of antidepressant medications has been associated with increased risk of fracture, but prior studies have been limited by incomplete control of confounders or a limited number of fractures. Use of antidepressant medications by 8,217 community-dwelling women aged 69 and older from a population-based prospective cohort study at four US clinical centers was assessed by interview at four examinations over a 10-year period, beginning in 1992–1994. Use was coded as a time-dependent variable. Incident fractures occurring after the initial medication assessment until July 2007 were confirmed by radiographic reports. Potential confounders were included in multivariable models and updated at each follow-up visit. Compared to nonusers of antidepressant medications, women using SSRIs experienced a higher risk of nonspine fracture in age-adjusted models (HR = 1.36, 95% CI 1.11–1.67) and in multivariable models controlling for potential confounders (HR = 1.30, 95% CI 1.04–1.62). SSRI use was not associated with an increased risk of first hip fracture (HR = 1.01, 95% CI 0.71–1.44) but was associated with an increased risk of wrist fracture (HR = 1.54, 95% CI 1.01–2.36). TCA use was associated with an increased risk of nonspine fracture in age-adjusted models, but in multivariable models this risk was attenuated. SSRI use was associated with a higher risk of any nonspine fracture, but not hip fracture, in this cohort of older women. TCA use was associated with a higher risk of nonspine fracture, but this association was in part explained by confounding factors.

This study is conducted for the Study of Osteoporotic Fractures Research Group

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Use of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), the two most widely prescribed classes of antidepressant medications, has been associated with an increased risk of fracture in some studies [1–12]. TCAs have been postulated to increase the risk of fractures due to an increased risk of falls, attributed to sedation and postural instability associated with these medications [13, 14]. SSRIs have also been associated with an increased risk of falls [14, 15], a possible mechanism for the observed association between SSRI use and risk of fracture. In addition, SSRI use has been linked to possible direct detrimental effects on bone metabolism and bone mineral density (BMD) [16–20].

The observed associations between SSRI use, TCA use, and risk of fracture, however, may also be due to potential confounders since antidepressant use is associated with poorer health status, poorer physical functioning, and other factors which are associated with an increased risk of fracture. In addition, confounding by indication may be an important cause of the observed association since the medications are often prescribed for depressive symptoms, which have been associated with lower BMD, increased risk of falls, and increased risk of fractures in some studies [21–35].

Previous work examining use of antidepressant medications and risk of fracture has often been limited by inadequate control of potentially confounding factors or a small number of fractures. Many previous reports have utilized claims databases, which have been limited in their ability to control for important confounders, such as weight, smoking status, health conditions, and depressive symptoms [4, 6, 10, 12]. To determine whether SSRI and TCA use among older women is associated with subsequent risk of fracture, we ascertained use of antidepressant medication, assessed evidence for depressive symptoms at each of four examinations, and contacted participants every 4 months to ascertain incident fractures over a 10-year period in women aged 69 years and older enrolled in the Study of Osteoporotic Fractures.

Materials and Methods

Participants

From 1986 to 1988, 9,704 women at least 65 years old were recruited for participation in the prospective Study of Osteoporotic Fractures. Women were recruited from population-based listings in Baltimore County, MD; Minneapolis, MN; the Monongahela valley, PA; and Portland, OR [36]. We initially excluded black women because of their low incidence of hip fracture, women who were unable to walk without help, and women with a history of bilateral hip replacement.

Between August 1992 and July 1994, 8,412 of the original cohort (93% of survivors) attended a fourth clinic examination (year 6). Between January 1995 and August 1996, 7,847 of the original cohort (95% of survivors) attended a fifth clinic examination (year 8); and from January 1997 to December 1998, 7,008 of the original cohort (93% of survivors) attended a sixth clinic examination (year 10). From January 2002 to April 2004, 4,261 women (75% of survivors) attended an eighth clinic examination (year 16).

Of the 8,412 women attending the year 6 exam, 8,127 completed a medication inventory at this exam. Of those who attended the year 6 exam, 7,385 had medication data at the year 8 visit, 6,340 had medication data at year 10, and 3,256 had medication data at year 16. A total of 8,217 women attended year 6 and had medication-use data for at least one visit from year 6 through year 16.

Women who reported use of a non-SSRI, non-TCA antidepressant or both an SSRI and a TCA at a visit were excluded from the analysis for the subsequent follow-up period. For example, those using both an SSRI and a TCA at year 8 were classified as missing for the portion of the analyses that used the year 8 medication data. In addition, for the analysis of SSRI use and risk of fracture, women were excluded from the analysis during any follow-up period in which they reported use of a TCA. For the analysis of TCA use and risk of fracture, women were excluded from the analysis during any follow-up period in which they reported use of an SSRI antidepressant.

The appropriate institutional review boards approved the study, and written informed consent was obtained from all participants.

SSRI and TCA Use

Participants were asked to bring all current (any use within last 30 days) prescription and nonprescription medications to each visit. Interviewers completed a medication history for each participant, including name of medication and frequency of use. A computerized dictionary was used to categorize type of medication from product brand and generic names obtained from containers [37]. Subsequently, a physician (S. J. D.) blinded to outcome status reviewed the computerized drug data for SSRI and TCA use and verified the classification of medications.

Nonusers were defined as women reporting no use of any type of antidepressant at a given visit. *SSRI users* were defined as women reporting SSRI use but no use of other

antidepressants at a given visit. *TCA users* were defined as women reporting TCA use but no use of other antidepressants at a given visit.

Ascertainment of Fractures

After the year 6 examination, we contacted participants about fractures every 4 months by postcard or telephone and were able to complete 95% of these contacts. All fractures were confirmed by radiographic reports. The primary fracture outcome "all nonspine fractures" included all nonvertebral fractures; in addition, secondary fracture outcomes included first hip fractures and wrist fractures. Average follow-up was 7.93 ± 4.64 years for nonspine fractures. In secondary analyses, we excluded fractures that occurred because of major trauma; because the results were not altered, we present the results from the primary analysis here.

Measurement of BMD

BMD of the total hip was measured at each examination using dual-energy X-ray absorptiometry with the Hologic QDR-1000 or Hologic QDR-2000 scanner (Hologic, Bedford, MA). Repeat measurements of hip BMD were performed on the same instruments used for the initial measurements. Further details of the measurement method, densitometry quality-control procedures, and precision of the measurements in our cohort have been published elsewhere [38, 39].

Depressive Symptoms

Depressive symptoms were evaluated using the 15-item Geriatric Depression Scale (GDS) [40], a self-report scale consisting of 15 yes-or-no questions regarding symptoms of depression. A standard cutoff of six or more symptoms was used to define evidence of depression; the cutoff point of six or more symptoms has a sensitivity of 88% and a specificity of 62% compared with a structured clinical interview for depression [41]. All analyses were performed using the total GDS score as a continuous variable as well as a dichotomized score of <6 vs. ≥ 6. As results were similar, analyses using the total GDS score are presented here.

Other Measurements

Participants completed a questionnaire and were interviewed at each examination and asked about self-reported health, physical activity, living situation, history of falls in the previous year, history of fractures since the age of 50, alcohol use, and smoking status. Current use of estrogen, thiazides, bisphosphonates, benzodiazepines, proton pump inhibitors, oral corticosteroids, vitamin D supplements, and calcium supplements was determined using the method described for ascertainment of antidepressant use.

To assess function, women were asked whether they had difficulty performing any of five independent activities of daily living (IADL) [42–44]. A composite functional impairment score expressed the total number of activities ranging from 0 to 5 that a participant reported difficulty performing. Cognitive function was assessed with the modified Mini-Mental State Examination (m-MMSE) (maximum score 26) [45]. Body weight was measured using a balance beam scale. Neuromuscular function was assessed by measuring the time in seconds needed to walk 12 m and determining whether the participant could rise from a chair (without using the arms) five times [46].

Statistical Analysis

χ^2 Tests for categorical variables, *t*-tests for normally distributed continuous data, and Wilcoxon rank sum tests for skewed continuous data were used to compare characteristics at the fourth examination by category of antidepressant use (nonusers vs. SSRI users, nonusers vs. TCA users).

To examine the association between SSRI use and risk of subsequent fracture, the hazard ratio (HR) and its 95% confidence interval (CI) for risk of fracture were calculated by category of SSRI use using Cox regression models. Similar analyses were performed to examine the association between TCA use and risk of fracture. Category of SSRI use and TCA use was updated at each exam. In addition, known risk factors for fractures in our cohort and characteristics related to antidepressant use were examined for inclusion in multivariable models for the associations between SSRI use and TCA use and risk of fracture. We included in our multivariable models age and those variables (health status, number of IADL impairments, walks for exercise, ability to rise from chair, m-MMSE score, smoking status, alcohol use, estrogen use, bisphosphonate use, benzodiazepine use, thiazide use, proton pump inhibitor use, oral steroid use, weight, GDS score, history of prior fracture, and total-hip BMD at year 6) that were related to SSRI use or TCA use at $P \leq 0.10$ or risk of nonspine fracture at $P \leq 0.10$ independent of age at year 6 ("base model"). All covariates, with the exception of total-hip BMD (obtained at year 6) and history of prior fracture, were updated at each follow-up visit in this base model. Missing values were set to the value from the most recent previous visit at which the data were available. To determine if change in BMD or falls mediated any association between antidepressant use and risk of fracture, we also examined multivariable models, updating total-hip BMD and history of falls in the previous year at each visit, in

addition to the covariates in the base model ("final model").

All analyses were performed using SAS software (version 9.1; SAS Institute, Cary, NC).

Results

Characteristics of the Study Population

At the year 6 examination (baseline exam in this analysis), the cohort included 8,127 women, of whom 91 (1.1%) were users of SSRIs and 340 (4.2%) were users of TCAs. Seventy women were on another class of antidepressant or were on both an SSRI and TCA and were excluded from the analysis between year 6 and year 8. By the year 16 examination (last exam for this analysis), 3,256 women completed a medication inventory and 280 (8.6%) were users of SSRIs and 90 (2.8%) were users of TCAs. There were 117 on another class of antidepressant or on both an SSRI and TCA and, thus, excluded from the analysis for the time period following year 16. Specific drug use among women taking SSRIs and TCAs at each exam is listed in Table 1.

Characteristics of the 8,057 participants at the year 6 examination according to category of antidepressant use are shown in Table 2. Compared with nonusers of antidepressants, users of TCAs and of SSRIs were more likely to score 6 or higher on the GDS. On average, they had a higher number of IADL impairments, were less likely to walk for exercise, and were more likely to have difficulty standing from a seated position. SSRI users were more likely to report poor health status. Both TCA users and SSRI users were more likely to report a fall in the previous year.

Prevalence of Fractures

Of the 8,217 women with medication-use data for at least one visit from year 6 through year 16, 2,809 experienced an incident nonspine fracture over the follow-up period, including 936 with a first hip fracture and 582 with a wrist fracture.

SSRI Use and Risk of Fracture

Risk of fracture, according to category of antidepressant use, is shown in Table 3. Women taking SSRIs experienced a higher age-adjusted risk of nonspine fracture compared with nonusers (HR = 1.36, 95% CI 1.11–1.67). Results were not substantially altered after adjusting for multiple potential confounding factors including age, health status, functional status, walking for exercise, ability to rise from chair, cognitive function (m-MMSE score), smoking status, alcohol use, estrogen use, bisphosphonate use, benzodiazepine use, thiazide use, proton pump inhibitor use, oral steroid use, weight, total-hip BMD at year 6, history of prior fracture, and GDS score (HR = 1.38, 95%

Table 1 Use of antidepressants

	Year 6	Year 8	Year 10	Year 16
Total attending the visit (*n*)	8,412	7,847	7,008	4,261
Total at visit of those who attended year 6 visit (*n*)	8,412	7,778	6,929	4,233
Total with medication inventory (*n*)	8,127	7,385	6,340	3,256
No antidepressant use (*n*)	7,626	6,824	5,738	2,769
SSRIs	91	171	217	280
Fluoxetine	43	47	43	37
Paroxetine	12	42	85	98
Sertraline	37	83	88	99
Citalopram	–	–	1	44
Escitalopram	–	–	–	3
Fluvoxamine	–	–	1	–
TCAs	340	300	262	90
Amitriptyline	167	149	147	56
Nortriptyline	53	47	42	11
Imipramine	48	46	35	8
Desipramine	12	7	10	2
Doxepin	59	53	30	13
Clomipramine	1	–	–	–
Trimipramine	1	–	–	–
Use of non-SSRI, non-TCA, or both SSRI and TCA	70	90	123	117

Table 2 Baseline (year 6) characteristics by category of antidepressant use

	Nonusers of antidepressants ($n = 7,626$)	TCA users ($n = 340$)	SSRI users ($n = 91$)
Age, years (mean ± SD)	77.01 ± 5.01	76.86 ± 4.75	77.25 ± 5.03
GDS score 0–15 (mean ± SD)	1.82 ± 2.23	2.95 ± 2.75*	4.26 ± 3.31*
GDS score ≥ 6, *n* (%)	448 (7.13)	52 (18.25)*	19 (29.23)*
Self-reported health status, *n* (%)			
Poor or very poor	194 (2.55)	13 (3.82)*	13 (14.44)*
Fair	1,342 (17.62)	100 (29.41)	31 (34.44)
Excellent or good	6,079 (79.83)	227 (66.76)	46 (51.11)
Weight (kg, mean ± SD)	66.37 ± 12.75	66.31 ± 13.31	62.76 ± 12.36*
0–5 IADL impairments (mean ± SD)	0.72 ± 1.27	1.33 ± 1.69*	1.84 ± 1.84*
Walks for exercise, *n* (%)	3,647 (48.09)	132 (38.82)*	32 (35.16)*
Lives alone, *n* (%)	3,697 (48.58)	170 (50.00)	44 (48.35)
Walking speed (m/sec, mean ± SD)	0.95 ± 0.23	0.85 ± 0.23*	0.89 ± 0.26*
Inability to rise from chair, *n* (%)	749 (11.73)	61 (20.89)*	17 (25.37)*
Current smoker, *n* (%)	444 (5.83)	26 (7.65)	9 (9.89)
Alcohol use (drinks/week, mean ± SD)	1.33 ± 3.14	1.12 ± 3.00*	0.90 ± 2.21
Current calcium supplement use, *n* (%)	3,074 (40.31)	150 (44.12)	30 (32.97)
Current vitamin D supplement user, *n* (%)	2,894 (37.95)	138 (40.59)	38 (41.76)
Current oral estrogen use, *n* (%)	1,254 (16.44)	97 (28.53)*	25 (27.47)*
Current thiazide use, *n* (%)	1,463 (19.18)	75 (22.06)	20 (21.98)
Current bisphosphonate use, *n* (%)	58 (0.76)	4 (1.18)	3 (3.30)*
Current benzodiazepine use, *n* (%)	531 (6.96)	55 (16.18)*	24 (26.37)*
Oral steroid use, n (%)	225 (2.95)	12 (3.53)	3 (3.30)
Proton pump inhibitor use, *n* (%)	64 (0.84)	6 (1.76)	2 (2.20)
Thiazolidenedione use, *n* (%)	No users V4	No users V4	No users V4
m-MMSE score 0–26 (mean ± SD)	24.45 ± 1.92	24.09 ± 2.19*	23.77 ± 2.24*
Fall in last year, *n* (%)	2,244 (29.48)	137 (40.29)*	41 (45.05)*
Number of falls in last year (mean ± SD)	0.52 ± 1.80	1.04 ± 2.32*	1.14 ± 2.23*
Previous nonspine fracture after age 50, *n* (%)	3,420 (45.08)	171 (50.44)*	46 (50.55)
Total-hip BMD (g/cm^2, mean ± SD)	0.74 ± 0.13	0.74 ± 0.14	0.75 ± 0.16

* $P < 0.1$ comparing SSRI users to nonusers and TCA users to nonusers

Note: *P* values for age, weight, walking speed, and total-hip BMD from *t*-test; *P* values for GDS score, IADL impairment, alcohol use, and m-MMSE from Wilcoxon rank-sum test due to skewness; *P* values for categorical variables from χ^2 test; *P* values for bisphosphonate use, oral steroid use, and proton pump inhibitor use from Fisher's exact test

CI 1.10–1.72). In addition, the association persisted in final multivariable models that included updated total-hip BMD at each visit and history of falls in previous year to the base model ("final model") (Table 3).

After adjustment for age alone, SSRI users had a 1.3-fold increase in the risk of hip fracture, which did not reach the level of significance (HR = 1.30, 95% CI 0.94–1.80). The magnitude of association was further attenuated after adjustment for multiple potential confounders (HR = 1.13, 95% CI 0.79–1.60) and close to 1.0 (HR = 1.01, 95% CI 0.71–1.44) after inclusion of updated BMD and fall history in the final model. SSRI users had a 1.42-fold increase in the risk of wrist fracture in age-adjusted models (HR = 1.42, 95% CI 0.94–2.14); this increase in risk of wrist fracture remained in the base and final multivariable models (HR = 1.64, 95% CI 1.05–2.56, for base model and HR = 1.54, 95% CI 1.01–2.36, for final multivariable model).

TCA Use and Risk of Fracture

Women taking TCAs experienced a higher age-adjusted risk of nonspine fracture compared with nonusers (HR = 1.38, 95% CI 1.16–1.64). In the multivariable base model, the association between TCA use and risk of nonspine fracture was attenuated and no longer reached significance (HR = 1.16, 95% CI 0.95–1.42); findings were similar using the multivariable final model, updating total-hip BMD and fall history at each exam (Table 3).

Table 3 Association between use of SSRIs and TCAs and risk of fracture

	HR (95% CI)		
	Age-adjusted model	Base model[a]	Final multivariate model[b]
SSRIs			
Nonspine fracture	1.36 (1.11–1.67)	1.38 (1.10–1.72)	1.30 (1.04–1.62)
First hip fracture	1.30 (0.94–1.80)	1.13 (0.79–1.60)	1.01 (0.71–1.44)
Wrist fracture	1.42 (0.94–2.14)	1.64 (1.05–2.56)	1.54 (1.01–2.36)
TCAs			
Nonspine fracture	1.38 (1.16–1.64)	1.16 (0.95–1.42)	1.16 (0.95–1.41)
First hip fracture	1.48 (1.10–1.98)	1.22 (0.86–1.74)	1.21 (0.86–1.69)
Wrist fracture	1.45 (1.01–2.08)	1.45 (0.96–2.18)	1.43 (0.97–2.13)

[a] Base multivariate model adjusted for age, health status, IADLs, ability to risk from chair, m-MMSE, smoking, alcohol use, estrogen use, bisphosphonate use, benzodiazepine use, thiazide use, proton pump inhibitor use, oral steroid use, weight, GDS score, walks for exercise, history of prior fracture, and total-hip BMD at year 6

[b] Final multivariate model includes base model plus updated total-hip BMD and history of falls in the previous year

TCA users had a 1.48-fold increase in the risk of hip fracture in age-adjusted models (HR = 1.48, 95% CI 1.10–1.98). In multivariable models adjusting for potential confounders (base model) the HR for risk of hip fracture was 1.22 (95% CI 0.86–1.74); results were similar for the final model including updated total-hip BMD and fall history (Table 3). TCA users had a 1.45-fold increase in the risk of wrist fracture in age-adjusted models (HR = 1.45, 95% CI 1.01–2.08; $P = 0.05$); results were similar in the multivariable models, though the 95% CI around the point estimate of the association slightly overlapped 1.0 (Table 3).

Effect of Depressive Symptoms on Association Between Antidepressant Use and Risk of Fracture

There was no evidence of an interaction between SSRI use and GDS score or between SSRI use and depression (defined by GDS score $\geq$6) for prediction of risk of nonspine fracture, hip fracture, or wrist fracture (P for interaction $\geq$0.34 in all age-adjusted models). Similarly, there was no evidence for an interaction between TCA use and GDS score for prediction of fracture risk.

Discussion

In this cohort of older women, those taking SSRIs and those taking TCAs had higher subsequent risks of any nonspine, hip, and wrist fractures. However, associations of SSRI use with hip fracture and associations between TCA use and fracture (including any nonspine and hip fracture) were in large part explained by potential confounding factors and did not persist in multivariable models. Other prospective cohort studies have also reported an increased risk of fracture with the use of SSRIs, including the observational cohort of the Women's Health Initiative, the Canadian Multicentre Osteoporosis Study, and the Rotterdam Study [2, 5, 7, 11, 47]. In addition, a prior analysis from the Study of Osteoporotic Fractures cohort indicated that use of any antidepressant medication was independently associated with a higher risk of nonspine fracture, including hip fracture [2]. A secondary analysis from the earlier study suggested that women using TCAs and women using SSRIs were at increased risk of fracture, but only the association between TCA use and hip fracture reached the level of significance. Our results are in general agreement with these findings, but this study differs from the prior analysis due to its longer duration of follow-up (10 vs. 4.8 years in the prior analysis) and updating of covariate status during follow-up. Due to temporal trends in antidepressant use, SSRI use was relatively infrequent in the earlier analysis, while TCA use was more prevalent. As a result, the prior analysis had low power to detect an association between SSRI use and risk of fracture but higher power to detect an association between TCA use and fracture risk.

Changing prescribing practices may explain our findings regarding TCA use and risk of fracture. In age-adjusted models, we observed an association between TCA use and nonspine fracture, as well as with hip fracture and wrist fracture. However, in multivariable models, we did not observe an association between use of TCAs and risk of nonspine fracture, a finding that differs from other work [2, 4–6]. TCAs are now less often prescribed for depressive symptoms and are more commonly used for the treatment of insomnia or chronic pain; for these indications they are often prescribed at lower doses than those used to treat

depression. Earlier work prior to the widespread use of SSRIs as a first-line treatment for depression would have been more likely to include subjects on substantially higher doses of TCAs.

There are several other potential explanations for our findings regarding TCA use and risk of fracture. Vestergaard et al. [10] found that only the most sedating TCAs (amitriptyline and clomipramine) were associated with risk of fracture in a large case–control study and that the risk of fracture was greatest within the first 6 months of starting therapy. As a result, the longer follow-up time in our analysis may have masked an effect of shorter-term TCA use on risk of fracture. In addition, we did not have sufficient numbers of TCA users to examine risk of fracture by specific TCA and, thus, analyzed both sedating and nonsedating TCAs together. In addition, we may not have observed an association between TCA use and fracture because the degree of 5-HT transporter inhibition differs among the many TCAs [48].

Due to the larger number of fractures in our analyses, we were able to examine the risk of some specific fractures, namely, hip and wrist fractures. We found that SSRI use was associated with an increased risk of wrist fracture but not an increased risk of hip fracture. These findings are similar to those in the Women's Health Initiative, which found an increased risk of "any fracture" and an increased risk of wrist fracture in SSRI users but did not observe a statistically significant increased risk of hip fracture (HR = 1.33, 95% CI 0.95–1.86; $P = 0.1$) [47]. Other prospective cohort studies to date have had an inadequate number of hip fractures to examine risk of hip fracture specifically [7, 11].

The lack of an association between SSRI use and hip fracture in our analysis differs from the results of several case–control studies using claims databases, which have reported an increased risk of hip fracture in SSRI users [4, 6, 10, 12]. However, claims database studies are markedly limited in their ability to control for potentially important confounders, such as depression status, BMI, physical functioning, and smoking status.

One potential explanation for the association between SSRI use and risk of nonspine fracture observed in this and other cohort studies is that SSRI use may have a direct adverse effect on bone metabolism [19, 20]. In vitro and in vivo laboratory investigations have documented functional serotonin (5-HT) receptors and serotonin transporter systems (5-HTT) in osteoblasts, osteoclasts, and osteocytes [48–50], raising the possibility that inhibition of these transporter systems may have effects on bone metabolism. Bone mass is reduced in mice with a null mutation for the gene encoding for the serotonin transporter, and young and adult mice treated with an SSRI demonstrate reduced bone mineral accrual and bone strength [18, 51, 52]. Warden et al. [53] observed both reduced bone-formation activity of osteoblasts and increased bone-resorption activity of osteoclasts in mice treated with SSRIs. On the other hand, other researchers have reported a possible anabolic effect of SSRIs on trabecular bone [54]. Recently, researchers have reported that decreased levels of gut-derived serotonin blood levels appear to increase bone formation in mice, while increased serotonin blood levels decrease bone formation, further suggesting a possible role for serotonin in bone metabolism [55].

Evidence in humans that blockade of serotonin reuptake has a negative effect on bone metabolism is inconsistent. Some observational studies have reported lower BMD and higher rates of bone loss in users of SSRIs relative to nonusers, despite controlling for potential confounders such as body mass index, self-reported health status, physical activity, depressive symptoms, and smoking status [7, 16, 17, 24, 56]. Other work, however, has not observed an association between SSRI use and lower BMD [47]. To our knowledge, no randomized controlled trial of SSRIs has included fracture ascertainment, measurement of BMD, or measurement of other bone parameters such as markers of bone turnover as an outcome.

Alternatively, use of antidepressants may be associated with increased risk of fracture due to an increased risk of falls as use of antidepressants may have a sedative effect [2, 7, 30]. Interestingly, addition of updated BMD and history of falls in the previous year to our models did not significantly alter our point estimates for the risk of nonspine fractures, suggesting that bone loss and fall risk may not explain all of the observed association, a finding similar to that of Richards et al. [7] in the Canadian Multicentre Osteoporosis Study.

Most importantly, observational studies examining a possible association between antidepressant use and fractures are subject to confounding, which may also explain our findings. In particular, confounding by indication may be an important issue. Antidepressants are often prescribed for depressive symptoms and depression itself has been associated with fractures [30]. Depressive symptoms have also been associated with higher rates of bone loss in this cohort [21]. In addition, individuals using SSRIs or TCAs may have poorer health status and therefore be more likely to fall. Due to concerns about the side effects of TCAs, SSRIs may be preferentially prescribed to patients perceived to be at higher risk for falls because of comorbidities; these comorbidities may also predispose them to higher rates of fracture, another potential source of confounding. To address these potential confounders, we adjusted for several factors including health status, functional status, and physical function, although unmeasured factors might explain our results.

We found an independent association between SSRI use and nonspine and wrist, but not hip, fractures in this cohort. SSRI use may be associated with nonspine fracture but not hip fracture for a variety of reasons. In this age group (women aged 69 years and older), risk of hip fracture may be largely due to other risk factors, namely, advancing frailty. Alternatively, the lack of an association between SSRI use and hip fracture may be related to differences in the distribution of cortical vs. trabecular bone at the hip compared to other nonspine sites.

This analysis has a number of limitations. Since our cohort consists of elderly women, we cannot extrapolate our findings to other populations. And because we lacked information on dose and duration of use of antidepressants in the cohort, we were limited in our ability to look for evidence of a dose effect of antidepressants on risk of fracture. Given the observational design, the possibility of residual confounding cannot be eliminated. However, this study has several strengths including large sample size, comprehensive assessment of fracture risk factors, long-term follow-up, and updated information regarding medication use and covariates at several examinations.

Our findings suggest that the use of SSRIs is independently associated with an increased risk of any nonspine fracture, a finding consistent with other observational cohort studies and case–control studies. Use of TCAs was also associated with an increased risk of nonspine fracture, although this association was at least in part explained by potential confounding factors. Given the recent description of serotonin transporters in bone and the accumulating evidence that SSRI use is associated with increased fracture risk, further investigation of SSRI use and its effects on clinically important bone outcomes is warranted. Although a randomized, placebo-controlled clinical trial of an SSRI with fractures as an outcome would be the strongest evidence of a clinically significant effect of SSRI use on bone health, such a trial would have insurmountable barriers. A meta-analysis of the existing observational studies, as well as continued efforts to explore the consistency of these findings in other cohorts, would be useful future steps for furthering our understanding of the possible effects of SSRI use on bone health.

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