Association Between Bone Mineral Density and Depressive Symptoms in a Population-Based Sample

Rocco D. Hlis, BS[a]; Roger S. McIntyre, MD, FRCPC[b]; Naim M. Maalouf, MD[c]; Erin Van Enkevort, PhD[a]; and E. Sherwood Brown, MD, PhD[a,*]

ABSTRACT

Objective: This analysis was conducted to determine the relationship between bone mineral density (BMD) and depressive symptoms in a population-based cohort.

Methods: Data were extracted from the second phase of the Dallas Heart Study (DHS-2), a large, multiethnic population sample in Dallas County, Texas, from September 1, 2007, to December 31, 2009. Depressive symptom severity was measured with the 16-item Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR_{16}), which is derived from *DSM-IV* major depressive disorder criteria. BMD was measured using dual-energy x-ray absorptiometry. Multiple linear regressions examined the relationship between QIDS-SR_{16} score and BMD controlling for age, body mass index, sex, ethnicity, smoking status, alcohol use status, serum 25-hydroxyvitamin D concentration, antidepressant use, and physical activity as measured by total vigorous and moderate metabolic equivalents. Subgroup analyses explored differences related to age.

Results: QIDS-SR_{16} score was not a significant predictor of either lumbar spine or total hip T-score ($\beta = -0.01$, $P = .61$ and $\beta = -0.02$, $P = .39$) in the overall population (n = 2,285). There was a significant negative interaction term between age and QIDS-SR_{16} group ($\beta = -0.01$, $P = .01$). In participants aged 60 years or older (n = 465), QIDS-SR_{16} score was a significant predictor of BMD at the lumbar spine and total hip ($\beta = -0.14$, $P = .003$ and $\beta = -0.12$, $P = .006$, respectively).

Conclusions: QIDS-SR_{16} score did not significantly predict BMD in the overall DHS-2 sample. There was, however, a significant association observed in participants aged ≥ 60 years. Results suggest that diagnosis and treatment of depressive symptoms may be of clinical importance in older individuals, a subgroup at high risk for osteoporosis and fractures.

J Clin Psychiatry 2018;79(3):16m11276
https://doi.org/10.4088/JCP.16m11276

[a]Department of Psychiatry, The University of Texas Southwestern Medical Center, Dallas, Texas
[b]Department of Psychiatry, the University of Toronto, Toronto, Ontario, Canada
[c]Division of Mineral Metabolism in the Department of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas, Texas
**Corresponding author:* E. Sherwood Brown, MD, PhD, Department of Psychiatry, UT Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, MC 8849, Dallas, TX 75390-8849 (Sherwood.Brown@UTSouthwestern.edu).

Osteoporosis is a common condition defined by decreased bone strength. Affecting an estimated 10.2 million US adults in 2010 with an additional 43.4 million exhibiting low bone mass, osteoporosis presents a significant public health concern.[1] Patients with osteoporotic fractures accrue substantial additional direct health care costs compared to those without fractures.[2] In addition to monetary concerns, older patients who experience fractures are at an increased risk of death. Effects on accrual of bone density are of importance, as a lower peak bone mass increases risk of osteoporosis later in life.[3] Moreover, it has been demonstrated that the odds of falling in older adults (≥ 60 years) with major depressive disorder (MDD) are greater than in people without depression.[4]

While many risk factors have been identified for osteoporosis, it is still unclear if MDD is a definitive risk factor. Extant evidence suggests an association between MDD and lower bone mineral density (BMD); notwithstanding, differences between studies in sample composition and design prevent firm conclusion.[5] A recent analysis[6] of 164,890 patients from a database in Taiwan demonstrated that people diagnosed with depression were 1.3 times more likely to develop osteoporosis. In agreement with a model demonstrating an association between osteoporosis and MDD, depressed patients exhibited an increased risk of fracture in a meta-analysis of cohort studies.[7] Significant confounders, such as the effect of concomitant antidepressants on BMD, have obscured conclusions in the face of multiple, possibly contributing physiological mechanisms (eg, hypothalamic-pituitary-adrenal axis dysregulation). Prior studies have used small patient samples, have not controlled for confounding factors, or have based conclusions regarding BMD on values assessed with ultrasound rather than dual-energy x-ray absorptiometry (DXA), sometimes on a single skeletal region. Although racial and ethnic differences in both rates of depression and BMD have been reported, these differences have not been explored, as prior studies have largely consisted of racially uniform cohorts.

We therefore conducted analyses using depressive symptoms as assessed by the 16-item Quick Inventory of Depressive Symptomatology—Self-Report (QIDS-SR_{16}) and BMD data from the Dallas Heart Study (DHS). The DHS includes an epidemiologic sample of Dallas County, Texas, with the exception of oversampling African American persons to allow for exploration of racial differences in health outcomes and risk factors.

METHODS

Participants

The DHS was designed as a representative multistage sample of individuals residing in Dallas County that was initiated July 1, 2000, and completed December 31, 2002.[8] African Americans were, however,

oversampled with the intention of examining social and biological risk factors for cardiovascular disease within that subpopulation. Potential participants were recruited in a 1:1 ratio of African American to non–African American. Although the study was designed to look at cardiovascular risk factors in a population, the presence of preexisting heart disease was not a factor in enrollment. A second phase of the Dallas Heart Study (DHS-2) was conducted from September 1, 2007, to December 31, 2009, that was inclusive of individuals from the initial DHS as well as spouses or family members of past participants, who were included due to attrition in the first wave of the DHS (ie, DHS-1). Thus, DHS-2 was demographically slightly different from DHS-1 (eg, a greater proportion of women than men were included). Participants ranged in age from 18 to 85 years.[9] A more detailed description of the methods employed in the DHS has previously been published.[10] The study was approved by The University of Texas Southwestern Medical Center Institutional Review Board, and DHS participants provided written informed consent. For more information regarding the DHS, please visit http://www.utsouthwestern.edu/research/translational-medicine/doing-research/dallas-heart/index.html.

This cross-sectional analysis was performed on participant data extracted from DHS-2. Our study examined 3,401 individuals who had participated in DHS-2. Of these participants, 1,116 were excluded based on missing data for any of the following variables: lumbar spine, total hip BMD, age, body mass index (BMI), sex, ethnicity, smoking status, alcohol use status, serum 25-hydroxyvitamin D concentration, antidepressant use, physical activity measured by total vigorous and moderate metabolic equivalents, and QIDS-SR_{16} score.

Variables

Depressive symptoms. Participants in the DHS-2 were provided with the 16-item QIDS-SR_{16} and instructed to rate specific symptoms of depression categorized on a scale from 0 to 3. Scores for each participant were summated in adherence to scoring guidelines provided at www.ids-qids.org. Scoring of the QIDS-SR_{16} divides the items into depression criteria defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*), resulting in scores ranging from 0 to 27. QIDS-SR_{16} scores were divided into 3 categories of depression severity based on the total scores generated: no symptoms or mild (0–5), moderate (6–10), and severe or very severe (11 and higher). The psychometric properties of the QIDS-SR_{16} have been previously reported by Rush et al.[11]

Bone mineral density. Bone mineral density was measured at the lumbar spine, hip, and non-dominant radius using a Hologic DXA instrument during the DHS-2 clinic visit at St. Paul University Hospital in Dallas. The Hologic DXA instrument has a weight limit of 350 pounds. Therefore, BMD of participants weighing more than the 350 pounds was not measured. BMD T-scores at the lumbar spine (L1–L4) and total hip were used in the current analysis. T-scores were calculated as the number of standard deviations away from the mean for 30-year old white women irrespective of age and ethnicity, as is conventionally calculated.[12]

Clinical Points

- This study examined the relationship between bone mineral density and current depressive symptom severity, a hitherto unresolved connection, in a population-based and racially and ethnically diverse sample.
- The findings suggest that the severity of current depressive symptoms is related to bone mineral density in older people, a population at high risk for osteoporosis, falls, and fractures.

Demographic information and predictors. Demographic information was self-reported in a 54-page questionnaire administered to participants during the DHS-2 visit. Covariates of interest in our study were age, BMI, sex, ethnicity, smoking status, alcohol use status, serum 25-hydroxyvitamin D concentration, antidepressant use, and physical activity (measured as total moderate and vigorous metabolic equivalents). Self-described ethnicity was divided into the following categories: non-Hispanic African-American, non-Hispanic Caucasian, Hispanic, and other. Antidepressant use, which has been implicated in decreased BMD[13] and increased fall risk,[14] was separated into 3 categories: selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) use, non-SSRI/SNRI use, or no antidepressant use. Self-described smoking status was divided into the following categories: current smoker, past smoker, and never smoker. Self-reported alcohol use status was divided into the following categories: current drinker, recent abstainer, and lifetime abstainer. 25-Hydroxyvitamin D data were analyzed from blood samples taken during DHS-2 and recorded in nanograms per milliliter (SI conversion factor for ng/mL to mmol/L: 2.49). The Multi-Ethnic Study of Atherosclerosis questionnaire was used to document usual activities performed by participants in a week (for more information regarding the Multi-Ethnic Study of Atherosclerosis questionnaire, please visit https://www.mesa-nhlbi.org). Physically demanding activities were then converted to metabolic equivalents (MET) using the Compendium of Physical Activities[15] and recorded as MET × (min/wk). BMI was calculated from body measurements taken at the UT Southwestern St. Paul facilities using the following formula: weight (kg)/height ^{s}quared (m^2).

Statistical Analysis

Demographic characteristics of DHS-2 subjects were summarized as mean (SD) or as proportions when indicated. Categorical variables were compared with χ^2 tests, whereas continuous variables were compared with independent *t* tests in IBM SPSS Statistics version 23.0.[16] Multiple linear regressions were then run to examine the relationship between depressive symptoms and BMD. Spine T-scores and total hip T-scores were set as dependent

variables in 2 separate analyses (see Table 2). In each analysis, predictor variables consisted of the following: age, BMI, sex, ethnicity, smoking status, alcohol use status, serum 25-hydroxyvitamin D concentration, antidepressant use, total moderate and vigorous MET score, and QIDS-SR_{16} group. To examine the impact age and sex had on the relationship between depression and bone density, separate moderation models were run using the PROCESS macro by Andrew F. Hayes.[17]

Specifically, the interaction between age and QIDS-SR_{16} group was examined with spine T-scores as the dependent variable and the same model was repeated examining the interaction between sex and QIDS-SR_{16} igroup. Whereas results justified a subgroup regression on participants ≥ 60 years of age to explore differences related to age, results did not justify exploration of male and female subgroups or sex-specific covariates (eg, menopausal status, estrogen supplementation).

RESULTS

Participants included in the final sample were significantly different from those excluded on some characteristics, including BMI, sex, ethnicity, serum 25-hydroxyvitamin D concentration, and total moderate and vigorous MET. Descriptive characteristics of the sample used in each analysis are detailed in Table 1.

Predictors accounted for 12.5% and 30.0% of variance observed in spine and total hip T-scores, respectively ($R^2 = 0.125$, $P < .001$ and $R^2 = 0.300$, $P < .001$). Age, BMI, and ethnicity significantly predicted for spine T-score. Age, BMI, ethnicity, smoking status, SSRI or SNRI use, and physical activity measured by total moderate and vigorous MET significantly predicted for total hip T-score. QIDS-SR_{16} group was, however, not a significant predictor of either spine ($\beta = -0.011$, $P = .61$) or total hip T-scores ($\beta = -0.016$, $P = .39$) in the sample as a whole. Multiple regression results are shown in Table 2.

The interaction term between age and QIDS-SR_{16} group was significant and negative ($\beta = -0.0111$, $P = .01$), suggesting that increasing age strengthens the relationship between QIDS-SR_{16} score and BMD. The interaction term between sex and QIDS-SR_{16} score was not significant in the entire sample or in participants aged ≥ 60 years ($\beta = .018$, $P = .85$ and $\beta = .160$, $P = .51$, respectively).

Table 1. Characteristics of DHS-2 Participants Included in and Excluded From the Analysis[a]

	Participants Included (n = 2,285)		Participants Excluded (n = 1,116)[b]		
Variable	n	%	n	%	*P* Value
Sex					.007
Male	894	39.1	430	44.2	
Female	1,391	60.9	543	55.8	
Ethnicity					.037
Non-Hispanic African American	1,180	51.6	480	49.9	
Non-Hispanic white	719	31.5	345	35.9	
Hispanic	339	14.8	115	12.0	
Other	47	2.1	21	2.2	
Antidepressants					.266
Yes	242	10.6	116	11.9	
SSRI/SNRI	192				
Non-SSRI/SNRI	50				
No	2,043	89.4	857	88.1	
QIDS-SR_{16} score					.582
None or mild (> 0 but ≤ 6)	1,550	67.8	642	66.0	
Moderate (> 6 but ≤ 10)	465	20.4	208	21.4	
Severe or very severe (> 10 but ≤ 27)	270	11.8	123	12.6	
Smoking status					.874
Current smoker	522	22.8	220	23.5	
Past smoker	508	22.2	211	22.5	
Never smoker	1,255	54.9	505	54.0	
Alcohol use status					.238
Current drinker	1,604	70.2	626	67.2	
Recent abstainer	481	21.1	215	23.1	
Lifetime abstainer	200	8.8	91	9.8	
	Mean	SD	Mean	SD	
Age, y	49.8	10.9	50.2	11.7	.352
Body mass index	30.7	6.6	32.4	9.1	< .001
Serum 25-hydroxyvitamin D concentration	43.4	21.9	41.5	21.3	.004
Physical activity (MET × [min/wk])	8,886.7	11,483.0	7,634.0	10,343.8	.004

[a]A total of 2,285 participants were analyzed and compared to 962 excluded participants. χ^2 Tests were used for all categorical variables, whereas independent *t* tests were used for continuous variables.
[b]The total number of participants excluded (n) changes as a result of missing data.
Abbreviations: MET = metabolic equivalents, QIDS-SR_{16} = 16-item Quick Inventory of Depressive Symptomatology—Self Report, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

In a separate multiple regression analysis on participants with age ≥ 60 years (Table 3), predictors accounted for 15.2% and 26.2% of variance observed in spine and total hip T-scores, respectively ($R^2 = 0.152$, $P < .001$ and $R^2 = 0.262$, $P < .001$). In this older subgroup, the QIDS-SR_{16} score was a significant predictor of BMD as measured by spine and total hip T-scores ($\beta = -0.138$, $P = .003$ and $\beta = -0.117$, $P = .006$).

DISCUSSION

In the large, multiethnic, population-based DHS-2 sample, depressive symptoms did not significantly predict BMD T-score at the lumbar spine and total hip after adjusting for covariates. However, in individuals over the age of 60 years, depressive symptoms were associated with a lower BMD T-score at the spine and total hip. Our results in the older population align with a recent meta-analysis[18] and implicate the clinical management of depressed elderly patients, as this population is especially prone to fracture.

The cross-sectional nature of the DHS-2 limits conclusions regarding direct causality of MDD on lower BMD in older individuals, but past research has provided possible mechanistic support for a relationship.

Table 2. Predictors of Bone Mineral Density by Multiple Linear Regression[a]

Predictor Variable (n = 2,285)	β (standardized coefficient)	*P* Value	95% Confidence Interval	
			Lower Bound	Upper Bound
BMD in spine (T-score); $R^2 = 0.125$, P < .001				
$QIDS\text{-}SR_{16}$ score	−0.011	.609	−0.105	0.062
Age	−0.096	< .001	−0.018	−0.007
Sex	−0.026	.211	−0.196	0.043
Ethnicity	−0.224	< .001	−0.474	−0.329
Body mass index	0.222	< .001	0.040	0.057
SSRI/SNRI	−0.031	.127	−0.364	0.045
Non-SSRI/SNRI	0.025	.201	−0.132	0.627
Smoking status	0.020	.330	−0.035	0.105
Alcohol use status	−0.020	.319	−0.134	0.044
Physical activity (MET × [min/wk])	−0.006	.780	0.000	0.000
Serum 25-hydroxyvitamin D concentration	−0.008	.692	−0.003	0.002
BMD in hip (T-score); $R^2 = 0.300$, $P < .001$				
$QIDS\text{-}SR_{16}$ score	−0.016	.394	−0.086	0.034
Age	−0.228	< .001	−0.028	−0.020
Sex	0.022	.234	−0.034	0.139
Ethnicity	−0.171	< .001	−0.299	−0.194
Body mass index	0.448	< .001	0.073	0.086
SSRI/SNRI	−0.055	.002	−0.379	−0.083
Non-SSRI/SNRI	−0.015	.395	−0.394	0.155
Smoking status	0.062	.001	0.036	0.137
Alcohol use status	−0.022	.232	−0.103	0.025
Physical activity (MET × [min/wk])	0.048	.008	0.000	0.000
Serum 25-hydroxyvitamin D concentration	−0.019	.328	−0.003	0.001

[a]Multiple linear regressions were performed on 2,285 participants ≥ 18 years of age for spine BMD and hip BMD. β Is a standardized coefficient. Confidence intervals given are related to an unstandardized coefficient.

Abbreviations: BMD = bone mineral density, MET = metabolic equivalents, $QIDS\text{-}SR_{16}$ = 16-item Quick Inventory of Depressive Symptomatology—Self Report, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Table 3. Predictors of Bone Mineral Density in Participants Aged ≥ 60 Years (n = 465) by Multiple Linear Regression[a]

Predictor Variable	β (standardized coefficient)	*P* Value	95% Confidence Interval	
			Lower Bound	Upper Bound
BMD in spine (T-score); $R^2 = 0.152$, $P < .001$				
$QIDS\text{-}SR_{16}$ score	−0.138	.003	−0.574	−0.122
Age	−0.026	.559	−0.044	0.024
Sex	0.186	< .001	0.313	0.908
Ethnicity	−0.177	< .001	−0.595	−0.192
Body mass index	0.262	< .001	0.044	0.094
SSRI/SNRI	0.019	.669	−0.381	0.593
Non-SSRI/SNRI	0.117	.009	0.238	1.636
Smoking status	−0.019	.678	−0.243	0.158
Alcohol use status	0.028	.534	−0.138	0.267
Physical activity (MET × [min/wk])	−0.012	.795	0.000	0.000
Serum 25-hydroxyvitamin D concentration	−0.011	.806	−0.008	0.006
BMD in hip (T-score); $R^2 = 0.262$, $P < .001$				
$QIDS\text{-}SR_{16}$ score	−0.117	.006	−0.377	−0.063
Age	−0.105	.011	−0.054	−0.007
Sex	0.090	.037	0.013	0.427
Ethnicity	−0.213	< .001	−0.492	−0.212
Body mass index	0.411	< .001	0.064	0.098
SSRI/SNRI	−0.003	.951	−0.349	0.328
Non-SSRI/SNRI	0.030	.467	−0.306	0.666
Smoking status	0.064	.144	−0.035	0.243
Alcohol use status	−0.048	.262	−0.221	0.060
Physical activity (MET × [min/wk])	0.012	.767	0.000	0.000
Serum 25-hydroxyvitamin D concentration	−0.047	.277	−0.007	0.002

[a]Multiple linear regressions were performed on 465 participants ≥ 60 years of age for spine BMD and hip BMD. β Is a standardized coefficient. Confidence intervals given are related to an unstandardized coefficient.

Abbreviations: BMD = bone mineral density, MET = metabolic equivalents, $QIDS\text{-}SR_{16}$ = 16-item Quick Inventory of Depressive Symptomatology—Self Report, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

The chronic state of stress that is characteristic of MDD is known to elevate cortisol and catecholamines by way of the hypothalamic-pituitary-adrenal axis. Cortisol has a direct effect on osteoblasts, decreasing bone formation activity.[19] At the same time, inflammatory markers such as interleukin-6, C-reactive protein, and tumor necrosis factor-α, which have been shown to be elevated in MDD, have concomitant stimulatory effects on osteoclasts.[19–21] The nuanced effects of age on bone formation and resorption are unclear, but their increasing imbalance with age places the elderly population at higher risk for low BMD. It is possible that a preexisting imbalance may amplify the effects of any neurochemical imbalances related to MDD that would otherwise be buffered. The pathophysiologic concepts presented may provide some basis for why participant age moderated the effect of depressive symptoms on BMD. Another possibility is that more sedentary lifestyle patterns related to depressive symptoms, such as decreased physical activity,[22] decreased exposure to sunlight, or increased tobacco or alcohol use, might contribute to decreased BMD in older persons. However, when smoking status, alcohol use status, serum 25-hydroxyvitamin D concentration, and physical activity were controlled for, the relationship between depressive symptom severity and BMD remained significant in participants aged ≥ 60 years. Some evidence suggests that use of SSRIs may be associated with decreased BMD.[13] In the current analysis, the relationship between depressive symptoms and BMD in individuals aged ≥ 60 years remained significant and negative after controlling for antidepressant use.

There are several methodological aspects to this study that limit inferences and interpretations that can be made. The gold standard for MDD diagnosis is a structured diagnostic interview.[23] Our analyses, however, relied on measurement of depressive symptom severity using the self-report QIDS-SR_{16} rather than an actual diagnosis of MDD. Although the QIDS-SR_{16} items are derived from *DSM-IV*, it is not a clinical diagnostic instrument for MDD. There was also no recorded duration of depressive symptoms available in the DHS-2. Longer or shorter durations of depressive symptoms may produce differing levels of effects on BMD considering proposed mechanisms. Another area of limitation in this study was in the analysis of antidepressant data. Data from the DHS-2 did not provide the duration of antidepressant use. A number of dietary factors, including calcium and protein intake, are well-known determinants of bone mineral density and osteoporosis risk.[24] Nutrition and various dietary compounds have been implicated in the onset, maintenance, and severity of depressive disorders.[25] Diet, however, was not assessed in the DHS. A self-report metric for physical activity was used in this study. The reliability of self-reported physical activity assessments has been previously questioned and may be an additional limitation.[26] A strength of the study is the large and ethnically diverse sample. To our knowledge, it is the largest multiethnic analysis to date that has explored the relationship between BMD (as measured by DXA) and depressive symptoms while controlling for multiple covariates. Many prior studies have not quantified BMD with data from DXA instrumentation.[6,27–30] Those that have used DXA have been fairly homogeneous in terms of either ethnicity or age.[18,31]

CONCLUSION

In our sample extracted from the DHS-2, depressive symptoms were not associated with BMD quantified by either spine or total hip T-scores. Depressive symptoms did, however, negatively affect both spine and total hip T-scores in participants ≥ 60 years old. Our results suggest depression may be a risk factor for lower BMD in individuals ≥ 60 years old, a population that is particularly vulnerable to osteoporosis. The findings suggest that it may be important to screen for depressive symptoms in older patients to potentially decrease the risk of osteoporosis and fractures. Subsequent monitoring and treatment of symptoms in older patients may be essential to healthy BMD and reduced fracture risk. It is important to note, however, that, to our knowledge, no data are yet available suggesting that antidepressant treatment improves BMD or decreases the risk of fractures. In fact, antidepressants may even increase fall risk in the elderly, and certain types have been shown to decrease BMD.[13,14] Research is needed on the impact of antidepressant and psychosocial treatments for depression, as well as standard treatments for osteoporosis prevention, on BMD in elderly depressed persons.

Submitted: October 11, 2016; accepted January 17, 2017.

Published online: August 22, 2017.

Potential conflicts of interest: **Dr Brown** reports grants from Forest and Sunovion and personal fees from Genentech. **Dr McIntyre** reports grants from Stanley Medical Research Institute, Lundbeck, JanssenOrtho, Shire, Purdue, AstraZeneca, Pfizer, Otsuka, and Allergan. **Dr McIntyre** serves on the advisory board for and collects speaking fees from Lundbeck, Pfizer, AstraZeneca, Eli Lilly, JanssenOrtho, Purdue, Johnson & Johnson, Moksha8, Sunovion, Mitsubishi, Takeda, Forest, Otsuka, Bristol-Myers Squibb, and Shire. **Drs Maalouf** and **Van Enkevort** and **Mr Hlis** have no conflicts of interest.

Funding/support: This work was supported in part by grant UL1TR001105 from the National Center for Advancing Translational Science, National Institutes of Health.

Role of the sponsor: The supporters had no role in the design, analysis, interpretation, or publication of this study.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the Center for Translational Medicine, The University of Texas Southwestern Medical Center and its affiliated academic and health care centers, the National Center for Advancing Translational Sciences, or the National Institutes of Health.

REFERENCES

1. Wright NC, Looker AC, Saag KG, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res*. 2014;29(11):2520–2526.
2. Viswanathan HN, Curtis JR, Yu J, et al. Direct healthcare costs of osteoporosis-related fractures in managed care patients receiving pharmacological osteoporosis therapy. *Appl Health Econ Health Policy*. 2012;10(3):163–173.
3. Bonjour JP, Theintz G, Law F, et al. Peak bone mass: facts and uncertainties. *Arch Pediatr*. 1995;2(5):460–468.
4. Stubbs B, Stubbs J, Gnanaraj SD, et al. Falls in older adults with major depressive disorder (MDD): a systematic review and exploratory meta-analysis of prospective studies. *Int Psychogeriatr*. 2016;28(1):23–29.
5. Cizza G, Primma S, Coyle M, et al. Depression and osteoporosis: a research synthesis with meta-analysis. *Horm Metab Res*. 2010;42(7):467–482.
6. Lee CW, Liao CH, Lin CL, et al. Increased risk of osteoporosis in patients with depression: a population-based retrospective cohort study.

Mayo Clin Proc. 2015;90(1):63–70.
7. Wu Q, Liu J, Gallegos-Orozco JF, et al. Depression, fracture risk, and bone loss: a meta-analysis of cohort studies. *Osteoporos Int*. 2010;21(10):1627–1635.
8. Kramer H, Toto R, Peshock R, et al. Association between chronic kidney disease and coronary artery calcification: the Dallas Heart Study. *J Am Soc Nephrol*. 2005;16(2):507–513.
9. Brown ES, Hughes CW, McColl R, et al. Association of depressive symptoms with hippocampal volume in 1936 adults. *Neuropsychopharmacology*. 2014;39(3):770–779.
10. Victor RG, Haley RW, Willett DL, et al; Dallas Heart Study Investigators. The Dallas Heart Study: a population-based probability sample for the multidisciplinary study of ethnic differences in cardiovascular health. *Am J Cardiol*. 2004;93(12):1473–1480.
11. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573–583.
12. Garg MK, Kharb S. Dual energy X-ray absorptiometry: pitfalls in measurement and interpretation of bone mineral density. *Indian J Endocrinol Metab*. 2013;17(2):203–210.
13. Sansone RA, Sansone LA. SSRIs: bad to the bone? *Innov Clin Neurosci*. 2012;9(7-8):42–47.
14. Marcum ZA, Perera S, Thorpe JM, et al; Health ABC Study. Antidepressant use and recurrent falls in community-dwelling older adults: findings from the Health ABC Study. *Ann Pharmacother*. 2016;50(7):525–533.
15. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of physical activities: a second update of codes and MET values. *Med Sci Sports Exerc*. 2011;43(8):1575–1581.
16. *IBM SPSS Statistics for Windows* [computer program]. Version 23.0. Armonk, NY: IBM Corp; 2014.
17. Hayes AF. Introduction to mediation, moderation, and conditional process analysis: a regression-based approach. 2013.
18. Stubbs B, Brefka S, Dallmeier D, et al. Depression and reduced bone mineral density at the hip and lumbar spine: a comparative meta-analysis of studies in adults 60 years and older. *Psychosom Med*. 2016;78(4):492–500.
19. Raisz LG. Physiology and pathophysiology of bone remodeling. *Clin Chem*. 1999;45(8 P t 2):1353–1358.
20. Haapakoski R, Mathieu J, Ebmeier KP, et al. Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. *Brain Behav Immun*. 2015;49:206–215.
21. Liu Y, Ho RC, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. *J Affect Disord*. 2012;139(3):230–239.
22. Schuch F, Vancampfort D, Firth J, et al. Physical activity and sedentary behavior in people with major depressive disorder: a systematic review and meta-analysis. *J Affect Disord*. 2016.
23. Mitchell AJ, Vaze A, Rao S. Clinical diagnosis of depression in primary care: a meta-analysis. *Lancet*. 2009;374(9690):609–619.
24. Mitchell PJ, Cooper C, Dawson-Hughes B, et al. Life-course approach to nutrition. *Osteoporos Int*. 2015;26(12):2723–2742.
25. Lang UE, Beglinger C, Schweinfurth N, et al. Nutritional aspects of depression. *Cell Physiol Biochem*. 2015;37(3):1029–1043.
26. Soundy A, Roskell C, Stubbs B, et al. Selection, use and psychometric properties of physical activity measures to assess individuals with severe mental illness: a narrative synthesis. *Arch Psychiatr Nurs*. 2014;28(2):135–151.
27. Rauma PH, Pasco JA, Berk M, et al. The association between use of antidepressants and bone quality using quantitative heel ultrasound. *Aust N Z J Psychiatry*. 2015;49(5):437–443.
28. Oikonen M, Hintsanen M, Laaksonen M, et al. Depressive symptoms are associated with lower bone mineral density in young adults with high job strain: the Cardiovascular Risk in Young Finns Study. *Int J Behav Med*. 2014;21(3):464–469.
29. Oh SM, Kim HC, Kim KM, et al. Association between depressive symptoms and bone stiffness index in young adults: the Kangwha study. *PLoS One*. 2013;8(7):e69929.
30. Oh SM, Kim HC, Ahn SV, et al. Association between depression and bone mineral density in community-dwelling older men and women in Korea. *Maturitas*. 2012;71(2):142–146.
31. Rosenblat JD, Gregory JM, Carvalho AF, et al. Depression and disturbed bone metabolism: a narrative review of the epidemiological findings and postulated mechanisms. *Curr Mol Med*. 2016;16(2):165–178.