2011

Selective Serotonin Reuptake Inhibitors and Bone Mineral Density in a Population of U. S. Premenopausal Women

Lori J. Peterson
University of Massachusetts Amherst

SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND BONE MINERAL DENSITY IN A POPULATION OF U.S. PREMENOPAUSAL WOMEN

A Thesis Presented

By

LORI JEAN PETERSON

Submitted to the Graduate School of the

University of Massachusetts Amherst in partial fulfillment of the

requirements for the degree of

MASTER OF SCIENCE

May 2011

Public Health

Biostatistics and Epidemiology

SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND BONE MINERAL DENSITY IN A POPULATION OF U.S. PREMENOPAUSAL WOMEN

A Thesis Presented

By

LORI JEAN PETERSON

Approved as to style and content by:

_____
Elizabeth Bertone-Johnson, Chair

_____
Lisa Chasan-Taber, Member

_____
Carol Bigelow, Member

_____
Edward J. Stanek III, Department Head
School of Public Health and Health Sciences

DEDICATION

The thesis presented here is dedicated with gratitude and love to my daughter, Athena A. Conway, my father Thomas C. Peterson, and my sisters Kristie and Cherie Peterson.

ACKNOWLEDGMENTS

I would like to thank my thesis chair, Elizabeth Bertone-Johnson for her dedication, patience, and forced time limits which, if not present, would have led to much procrastination. I would also like to thank committee member Lisa Chasan-Taber, who was willing to read at least four versions of everything submitted with extreme patience and much needed constructive criticism. I extend a special thank you to my final committee member Carol Bigelow for giving me the confidence to pursue this degree, and a special note of appreciation is extended to Brian Whitcomb for his ability to speak epidemiology in a language that just made sense.

ABSTRACT

SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND BONE MINERAL DENSITY IN A POPULATION OF U.S. PREMENOPAUSAL WOMEN

MAY 2011

LORI J PETERSON, BA, UNIVERSITY OF MASSACHUSETTS, BOSTON

M.S., UNIVERSITY OF MASSACHUSETTS AMHERST

Directed by: Professor Elizabeth R. Bertone-Johnson

Low bone mineral density (BMD) in post-menopausal women is a risk factor for bone fractures and osteoporosis development. Prior studies in post-menopausal women have shown the use of antidepressant medications, specifically selective serotonin reuptake inhibitors (SSRIs) to be inversely related to BMD. However, the association has not been studied in pre-menopausal women. Current SSRI use is widespread with 8% of U.S. women age 18-44 reporting use. We evaluated the association between SSRIs and BMD and bone mineral content (BMC) cross-sectionally using data from the University of Massachusetts Vitamin D Status Study. SSRI use, diet, and lifestyle factors were assessed by questionnaire. BMD and BMC were measured using dual-energy x-ray absorptiometry (DEXA). The study included 256 women aged 18-30 (mean=21.6 years, SD=4.3 years). In this population, SSRI use was 5%, BMD values ranged from 0.97-1.38 g/cm^2 (mean 1.16, SD 0.08), and BMC values ranged from 1833g to 3682g (mean 2541.5, SD=349.2). After adjustment for age, body mass index, and physical activity, mean BMD in the 13 users of SSRIs was 1.15g/cm^2 (SD=0.06) compared to 1.16g/cm^2 (SD=0.77) in the 243 non-users (p =0.66). After the same adjustments, mean BMC in

the 13 users was 2467.1g (SD=285.0) compared to 2547.6g (SD=352.6) in the 243 non-users (p=0.94). Our findings do not support an inverse association between SSRI use and BMD or BMC. However, given the prevalence of SSRI use in young women and the potential for adverse effects on bone health, further study of this association is warranted.

TABLE OF CONTENTS

Page

LIST OF TABLES

CHAPTER I

INTRODUCTION

Low bone mineral density (BMD), also known as osteopenia, is a condition defined by the World Health Organization (WHO) as a change in BMD of between 1 standard deviation (SD) and 2.5 SD below the mean BMD of a healthy young adult.[10] In 2005, an estimated 49% of post-menopausal women met the WHO definition of low BMD, translating to 22.7 million women over the age of 50 with the condition.[10] Low BMD is a risk factor for future development of fractures and osteoporosis in older populations.[11] These conditions are projected to affect 14 million U.S. men and women and cost nearly 25 billion dollars per year.[5]

There are no statistics available on the prevalence of low BMD in premenopausal women, specifically those women age 18-30. Women in this age category are thought to have achieved peak bone mass. However, depression and anorexia nervosa have been shown to negatively affect BMD.[5, 16] According to the National Institutes of Mental Health, depression is most common in women aged 25-44 and anorexia is most common in women aged 15-19 with a prevalence of 0.5-1%. [16] These conditions are both treated with antidepressant medications. The most widely used class of antidepressants in the U. S. is known as selective serotonin reuptake inhibitors or SSRIs. Indeed, up to 8% of women, aged 18-44, in the U.S. report using this class of medications.[19]

SSRIs work by inhibiting the reuptake of serotonin in the central nervous system, effectively blocking the serotonin transporter and making more serotonin available to the central nervous system and potentially relieving the symptoms of depression.[7] The mechanism for how SSRI use leads to low BMD is unclear.[7] However, recent

experimental studies have discovered serotonin receptors and transporters in the bones of chickens and mice.[2, 20, 21] Serotonin and its transporters are believed to enhance fibroblast cell proliferation, increase activity in clonal osteoblasts, and alter the intensity in the response of osteoblasts to stimulation.[20] If the inhibitory action of SSRIs leads to a reduction in osteoblast activity and a reduction in the coupling activity of osteoblast and osteoclasts, this could be the mechanism by which SSRI use leads to low BMD. [8]

There have been no studies that have evaluated the effect of SSRI use on BMD in women ages 18 to 30. However, the association has been studied in post-menopausal women and men. Three prospective cohort studies, [15, 17, 18] four cross-sectional studies, [3, 9, 11, 22] and one longitudinal study [6] have been conducted. Use of SSRIs increased the risk of low BMD in all but two[11, 18] of these studies. The age range for the studies was 54-82 years of age with only the Third National Health and Nutritional Examination Survey (NHANES III) [11] including women as young as 29, however still above college age.

Because there is evidence supporting the association between SSRI use and low bone mineral density in older women, and low BMD is an established risk factor for fractures and osteoporosis, it is important to determine if using SSRIs earlier in life also leads to earlier negative effects on BMD. Such findings would identify an earlier predictor of fractures and osteoporosis. We conducted a cross-sectional analysis of SSRI use and BMD using data from the University of Massachusetts Vitamin D Status Study conducted among women aged 18-30.

CHAPTER II

PHYSIOLOGY OF SSRIS AND BONE MINERAL DENSITY

The biological mechanism for how SSRI use could lead to low BMD is not well understood,[8] however there are several possible pathways. Understanding how the medication works and how it is related to bone mineral density requires understanding how serotonin works in the body, its specific cell processes, and recognition of new evidence for serotonin pathways in bone.

In the central nervous system, serotonin is responsible for regulating behavioral, physiological, and cognitive functions.[14] Serotonin synthesis begins with an uptake of an amino acid called tryptophan. Tryptophan is taken into the neuron and through enzymatic action is transformed into serotonin.[4] Serotonin is accumulated by the vesicular monoamine transporter 2 (VMAT2), which assists the neurons in the release of neurotransmitters. Serotonin is then stored in neural vesicles until it is needed and released by the vesicles. Once released the serotonin action can be stopped by the reuptake action of serotonin transporters.[4] SSRI antidepressant medications act in a similar manner by inhibiting the transporter,[6] leading to an increase in the level of extra-cellular serotonin in the central nervous system and thereby decreasing the depressive symptoms in patients.[7]

The mechanism by which SSRI may impact BMD is suggested by the finding that functional serotonin receptors and transporters have been identified in the bone of chickens and mice.[2, 20, 21] Serotonin is thought to aid in some functions of the osteocytes and assist in remodeling and repair of bone through osteoblast cell proliferation.[20] The main action of SSRI's is to block the serotonin transporters and increase the level of

extra-cellular serotonin. [7] The blocking of serotonin transporters in the central nervous system may help to alleviate symptoms of depression; however in the skeletal system this same action may lead to a reduction in osteoblast activity and a reduction in the coupling activity of osteoblasts and osteoclasts, both necessary for bone remolding. Once there is insufficient serotonin to carry out these necessary functions, the bones may be unable to complete remolding and adverse changes in bone density may be seen.

In summary, the actual pathways by which SSRI's lead to low BMD are not well understood. Recent identification of serotonin receptors and transporters in osteoblasts and osteocytes suggests a possible mechanism. However, further research is needed to fully understand the biological mechanism and its potential implications.

CHAPTER III

EPIDEMIOLOGY OF SSRIS AND BONE MINERAL DENISTY

The epidemiological evidence for the association between SSRI use and low BMD is limited with only seven observational studies conducted.[6, 9, 11, 15, 17, 18, 22] Previously, several studies have evaluated SSRI use in conjunction with the association between depression and low bone mineral density, [3, 6, 9, 11, 15, 17, 18, 22] or in conjunction with an association between depression and risk of fractures, [17, 18] Among the studies focusing on SSRI use and low BMD, two included only older men, [3, 9] three included male and female participants, [11, 15, 17] and three focused on women only.[6, 18, 22] Overall the findings have been consistently positive for an inverse association between SSRI use and BMD with four of the studies finding an increased risk of low BMD, [6, 9, 17, 22] two studies finding no association, [11, 18] and one study finding an increased risk for women but not for men.[15]

The three studies in women focused on post-menopausal women age 42-82 and shared several methodological aspects. First, all studies measured BMD using a Dual Energy X-ray Absorptiometry scanner (DEXA). Second, all studies adjusted for depression. Third, SSRI use was determined by asking women to bring their current medication to the interview, where the medication was typed, recorded, and subsequently confirmed by medical personnel. Forth, all measured BMD at specific sites, including femoral neck, mid forearm, trochanter, and total body. Finally, each study adjusted for the following covariates: age, race, weight, height, smoking, calcium use, menopausal status, health status, and physical activity.

In the first of these studies, Williams et al.[22] conducted a cross-sectional analysis of 128 women aged 42-61 in the Geelong Osteoporosis Study in South Eastern Australia between the years 1994-1997. Women included in the analysis had a lifetime history of depression as measured by the research version of DSM-IV-TR structured clinical interview. For those women who used SSRIs compared to those who do not and at each BMD site measured, the researchers found a lower percent of BMD: femoral neck was 5.6% lower, [0.977 (0.116) vs. 0.922 (0.117) p=0.03], trochanter was 6.2% lower, [0.813 (0.105) vs. 0.763 (0.107) p=0.04], and mid forearm was 4.4% lower, [0.745 (0.007) vs. 0.712 (0.068) p=0.03]. The strength of the study was adjusting for depression as a confounder.

Diem et al.[6] conducted a longitudinal study among 2,722 women aged 74-82 from the Study of Osteoporotic Fractures (SoOF) during the years 1997-1999. The study was conducted in four U. S. sites including; Maryland, Minnesota, Oregon, and Pennsylvania. In addition to the above listed covariates the study also adjusted for vitamin D intake, ability to rise from a chair, walking speed, use of oral estrogens, use of thiazide, bisphosphonate, and mini-mental state exam. Among users of SSRIs there was a 1.6 times greater rate of loss in BMD in all sites scanned, compared to non-users of SSRIs. The mean adjusted rate of bone loss per year for users at total hip was [-0.82% (95% CI=-1.00, -0.64)], at the femoral neck was [-0.60% (95% CI=-0.84, -0.36)] and at trochanter [-0.93% (95% CI=-1.18, -0.68)]. The strength of the study was the adjustment for depression and estrogen use; both have been theorized to play a role in bone health.

Spangler et al. conducted a prospective cohort study of women aged 50-79, enrolled in the Women's Health Initiative Study during 1994-1998. BMD measures were

collected on a subgroup of participants (14%) at baseline. Only those women who had complete information on at least one site were included in the analysis (hip=4539, 70% spine=4417, 69% total body=4502, 69%). This study examined use of SSRIs exclusively. The authors found no association between the use of SSRIs and 3-year changes in BMD.[18] [.003 (-0.0005 to .0069) p=0.09], [.002 (-.0031 to .0078) p=0.40], [.003 (-0.0007 to .0073) p= 0.10] in hip BMD, spine BMD, and total body BMD, respectively, compared with nonusers.

In summary, several studies have examined the association between SSRI use and BMD in women. Two of these three studies found that SSRI use increased the risk of adverse changes to BMD. No studies have examined the association in a population of young women aged 18-30.

CHAPTER IV

SUMMARY

Low BMD is a known risk factor for the development of fractures and osteoporosis. Low BMD is highly prevalent in older populations; with 49% of postmenopausal women meeting the WHO criteria.[10] SSRIs are widely used in young women age 18-30 with nearly 8% reporting use. It is unknown whether use of SSRIs affects BMD in young women at or near peak bone mass.

Recently, receptors and transporters for serotonin have been identified in bone, [2, 20, and 21] leading to the hypothesis that the inhibitory action of SSRIs may have an adverse effect on bones.[7]

Three epidemiological studies have focused on the relationship between SSRI use and BMD in women. Of these studies, two have found an increased risk and one observed a null finding. No epidemiological studies have examined the relationship in women age 18-30.

Therefore, we studied the association between SSRI use and BMD in women age 18-30, with a cross-sectional analysis of the data from the University of Massachusetts Vitamin D Status Study. We proposed that there is a negative association between SSRI use and BMD in this population.

CHAPTER V

HYPOTHESIS AND SPECIFIC STUDY AIM

Using a cross-sectional study design, the goal of this study was to determine if there is an association between the use of SSRI medications and changes in BMD among premenopausal U.S. women aged 18-30.

Using the same study data we conducted a secondary analysis of the relationship between history of depression and BMD.

Hypothesis 1: Women who use SSRI medication have lower BMD or BMC compared with women who do not use SSRI medication.

Hypothesis 2: Women who have a history of depression have lower BMD compared with women who do not have a history of depression.

CHAPTER VI

METHODS

VI. A. Study Design and Population

We conducted a cross-sectional study of SSRI use and BMD using data collected from the University of Massachusetts Vitamin D Status Study. The Vitamin D Status Study began in March of 2006 and is on-going. This analysis utilized data collected from participants enrolled as of February 2011. To be eligible, study participants had to be female, age 18-30, premenopausal, menstruating regularly, and residing in the local area surrounding the University of Massachusetts, Amherst, MA.[1] For the purposes of this analysis we used the previously defined exclusions. Women were ineligible if the reported any of the following conditions: high blood pressure, elevated cholesterol, kidney disease, liver disease, osteomalacia, digestive disorders, rheumatologic disease, multiple sclerosis, thyroid disease, hyperparathyroidism, cancer, diabetes, or polycystic ovaries. [20] Women with a history of using any of the following medications were also excluded: corticosteroids, anabolic steroids, anticonvulsants, cimetidine, and propranolol. Because the purpose of these exclusions is to focus the effect of SSRI medication only, we excluded those women who reported use of antidepressants other than SSRIs. These include: monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, tranquilizers, and lithium. The following brands were considered SSRIs for our analysis: Prozac, Zoloft, Paxil, or Effexor. In addition, if a study participant did not have a completed DEXA scan, she was excluded. DEXA scans were not available in the very early months of the study and therefore resulted in the exclusion of 10 women.

Eligible participants were scheduled to complete all study requirements in a single visit. In both phases of the study, the visit was required to occur during the luteal phase of each woman's menstrual cycle.[25] However, since the timing of ovulation is not relevant to the use of SSRIs or bone mass we did not consider luteal phase in the current analysis. During the visit, the women completed a questionnaire assessing lifestyle factors, a modified version of the Harvard Food Frequency Questionnaire (FFQ), provided a blood sample, and received a total body DEXA scan to measure BMD and bone mineral content (BMC).[1, 25]

VI. B. Assessment of Exposure

We measured the use of SSRIs with a self-administered questionnaire. One question was used to determine if the women were currently using SSRIs. The question was: "Are you currently taking any of the following medications? Mark all that apply." SSRI was the second choice on the list. Those women who marked "yes" to the SSRI choice were considered exposed. A women could have marked "yes" to SSRIs and "yes" to either "use of antacids" or "other medications" and still be considered exposed as long as the other medication was not another type of antidepressant, an anticonvulsant, a tranquilizer, or lithium. If a woman marked one of the following choices alone she was considered unexposed: "not taking any medications", "tranquilizers", "migraine prevention", or "other medication". In this analysis, current use of SSRIs was dichotomized as use or no use.

We measured history of depression using the same self-report questionnaire. The women were asked if they had ever been clinician-diagnosed with depression. If the women answered "yes" they were considered exposed.

VI. C. Validity of the Exposure Assessment

Self-report for antidepressant medications, including SSRIs, was previously validated by Kwon et al.[12] using pharmacy claims as the gold standard. The study participants lived in the Boston, MA area and were recruited from one of 9 area medical centers. The authors used 3 measures of antidepressant use. The first two measures were the following questions; "Do you now take any prescription medicines for depression?" and "Are you now taking prescription medicine for depression?" The data on pharmacy claims was obtained through access to medical records via Tufts Health Plan. Antidepressant use was defined as "the appearance of any claim for an antidepressant within the 90 days preceding a patient survey date." Self-report and pharmacy claims matched in 85% of cases with a kappa of 0.69.

VI. D. Assessment of Outcome

BMD and bone mineral content (BMC) were measured using total body DEXA scans. BMC was analyzed as another measure of bone health in the participants. Due to the age group, our population is at or near the peak levels of BMD; therefore, we determined the mean differences in BMD and BMC across the population. BMD was measured in g/cm^2 and reported as the areal BMD. Areal BMD refers to the surface area of the bone. This is in contrast to using bone mineral apparent density (BMAD), which measures volume of the bone. BMC was measured in grams and reported as the total bone content. The DEXA scanner is a narrow angle fan GE Lunar Prodigy scanner (GE Lunar Corp. Madison, WI), which was calibrated daily according to manufacturer instructions and all scans were carried out by two, trained technicians. All scans were analyzed using the manufacturer provided enCORE 2002 software, version 6.80.002.[25]

VI. E. Validity of Outcome Assessment

The validity of DEXA scans to measure BMD and BMC has been established in numerous studies.[3, 9, 11] In addition, DEXA is used by the Centers for Disease Control and Prevention (CDC), as part of the National Health and Nutrition Examination Survey (NHANES) studies.[11] Melton et al. found the correlations between whole body sites versus site-specific were good for most sites with the correlation between total body and site-specific as follows: 1) spine r^2=0.84; 2) Lumbar spine r^2=0.93; 3) Pelvis region r^2=0.74. [14]

VI. F. Assessment of Covariates

Information on lifestyle, demographic, and potential risk factors was collected using a self-report questionnaire completed at the same time as the DEXA scans, food frequency questionnaires, and SSRI use. We collected information on the following variables: history of depression, oral contraceptive use, age, smoking, alcohol consumption, race, age at onset of menstruation, and prior pregnancies. The amount of physical activity per week was calculated for each woman based on answers to several questions on the lifestyle questionnaire. A total physical activity score was obtained and reported as MET-hours per week of activity.[1] Calcium and vitamin D intake were assessed using FFQ (a modified version of the Harvard FFQ). Finally we collected height and weight information from the women and calculated her BMI (BMI=weight (kg)/height (m^2)).

VI. G. Univariate Analysis

All analyses were performed using SAS software version 9.2, (SAS Institute Inc, Cary, North Carolina.)

The frequency and percent of subjects based on distribution of SSRI use was calculated, as well as the distribution of the mean and SD of BMD and BMC in the population.

VI. H. Bivariate Analysis

We cross-tabulated the covariates by the exposure and the outcome to identify any potential confounders. For exposure by continuous variables (i.e. age, BMI, physical activity, BMD, calcium, and vitamin D) mean and standard deviations were calculated, and for exposure by categorical variables (parity, alcohol use, current oral contraceptive use, current smoking, tertiles of calcium and vitamin d use, dichotomized vitamin D use, history of depression, and dichotomized age at menarche) we calculated frequencies, relative frequencies, percents, and p-values from Fisher's Exact tests due to our small cell counts.

For outcome by continuous variables, we calculated differences in BMD per one unit change in the continuous covariate along with standard errors (SE) using general linear models. For outcome cross tabulated with categorical variables, means and SDs were calculated using one way ANOVAS. Differences in the distributions are presented by p-values from a two-sided t test.

VI. I. Multivariate analysis

We conducted three separate analyses. In the first we determined the relationship between SSRI use and BMD. In the second we determined the relationship between SSRI use and BMC, in the third we looked at history of depression as a predictor of BMD in the population. All analyses were conducted using linear regression models. Any potential confounders were included in the final model if the change between the

unadjusted and adjusted β-coefficient was 10% or more. Final, fully adjusted mean differences in BMD and BMC were calculated using least squares methods.

CHAPTER VII

HUMAN SUBJECT PROTECTION

All study participants signed a written informed consent prior to enrolling in the study and any collection of data. The women read the consent form in the presence of study staff and were given opportunity to express their concerns. If the participant agreed then she and the staff member both signed the consent form. All signed consent forms were stored at the study center in a binder.

Each study participant's personal information is kept confidential in the following manner: subject name and contact information are stored in files separately from study data. Subjects were given a study identification number and it is this number that accompanies all participant information. Any study information that is stored on a computer is password protected. No identifying information was or will be published in the future. Access to study data is restricted to the primary investigator and study staff. All study staff underwent institutional review board confidentiality training prior to accessing data.

The risks to the participants were minimal with only the slight pain or bruising associated with a needlepoint injection, from the blood draw. There is a minimal risk of infection from the needle stick, although this should be minimized by the use of single-use equipment. The low-dose radiation from the DEXA scanner is minimal, equivalent to the dose received from an airplane trip from Boston to Los Angeles, CA.

We conducted non-beneficial research, or research with no therapeutic benefit to the study participants. However, the women received information on the density of their

bones, fat mass, body composition, and vitamin D levels. This may highlight for them any medical issues and perhaps lead to beneficial lifestyle changes.

CHAPTER VIII

PERMISSION TO ACCESS DATA

I, Lori J Peterson, have completed and passed the Human Subject's Training through the Collaborative Institutional Training Initiative (CITI) registered with the University of Massachusetts Amherst. I have been granted permission to access the UMass Vitamin D Status Study by the Co-Principle Investigator, Elizabeth Bertone-Johnson, for the purpose of this thesis.

Signed:

_____

Dr. Elizabeth Bertone-Johnson

CHAPTER IX

RESULTS

In this population of pre-menopausal women the average age was just over 21 years (mean 21.6 years, SD=4.28 years (Table 1)). Most women averaged a low amount of daily physical activity and were in the normal range of BMI (mean 22.99 kg/m², SD=3.29). Most women also had levels of calcium intake below the recommended daily intake of 1300mg and levels of vitamin D intake below the daily recommended intake of 20ng/ml. (78% and 85% respectively). Additionally, few women had been pregnant (3%), were heavy alcohol consumers (23%), or were smokers (5%), The majority of participants considered themselves to be white race (86%), had not previously suffered from depression (87%), and were younger than 14 at menarche (79%).

Self-reported use of SSRI medications was low with only 13 or 5% of study participants reporting use (Table 2). The mean BMD of the population was 1.16 g/cm² (0.08) (Table 3), with a range of 0.97g/cm² to 1.38 g/cm². The distribution of BMC had a mean of 2541.5g (349.2) with a range of 1833g to 3682g. At the onset of the study in 2006, 10 women were enrolled prior to the availability of the DEXA scanner; as a result these ten (4%) women were unable to complete the scans and were therefore not included in the analysis.

Women who reported using SSRIs were not significantly different from those not using the medication with respect to age, BMI, physical activity, calcium or vitamin D intake, having been pregnant, use of contraceptives, race, or age at menarche (Table 4). However, users and non-users were significantly different with respect to history of

depression, with 85% of SSRI users reporting depression compared to only 10% of nonusers (p=<.001).

BMI and physical activity were the most statistically significant predictors of BMD (Table 5). For each one unit (kg/m²) change in BMI, BMD was .009g/cm² higher (SE=0.0014, p=<.0001), and for every one unit (1 hour of METS per week) change in physical activity BMD was 0.0002g/cm² higher, (SE=0.00007, p=0.0007). History of pregnancy, use of alcohol, current smoking or contraceptive use, race, various intake levels of calcium or vitamin D, history of depression, or age at menarche were not associated with BMD. BMI and physical activity were positively associated with BMC (Table 6). For every one unit (kg/m²) change in BMI, BMC was 45.6g higher, (SE=6.12, p=<.0001), and for every one unit (1 hour of METS per week) change in physical activity BMC was a 0.8g higher, (SE=0.33, p=0.02).

In unadjusted models estimating the relationship between SSRI use and BMD (Table 7), mean BMD in SSRI users (1.16 g/cm², SD=0.06) did not differ significantly from non users (1.17 g/cm² SD=0.08), (p=0.78). In unadjusted models mean BMC in SSRI users did not differ significantly from non users (2549.5g, SD=285) compared with (2541.1g SD=352.6) in non-users, (p=.94).

In analysis adjusted for age, SSRI use remained not associated with BMD or BMC (table 8). Results further adjusted for BMI and physical activity were similar for each outcome. The adjusted mean BMD in users of SSRIs was 1.15g/cm² and non-users was 1.16g/cm², (p=0.66). Use of SSRIs was associated with a -0.0094g/cm² lower bone mineral density. The adjusted mean BMC in users was 2467.1g and in non-users was

2547.6g, (p=0.39). Use of SSRIs was associated with a -80.4g lower bone mineral content.

In a secondary analysis estimating the association between history of depression and BMD and BMC, 33 (12.9%) women reported a history of depression (Table 9). The mean BMD for women with a history of depression was 1.17g/cm² (SD=0.08) compared to 1.16g/cm² (SD=0.08) in women without. In unadjusted and models adjusted for age, BMI, and physical activity there was no evidence of an inverse relationship between history of depression and BMD, (p=0.29) (Table 10). History of depression was associated with a 0.015g/cm² lower bone mineral density.

CHAPTER X

DISCUSSION

X. A. Main Study Findings

In this small cross-sectional study of women age 18-30, we found no evidence of an association between selective serotonin reuptake inhibitor (SSRIs) use and bone mineral density (BMD) or bone mineral content (BMC). There was also no evidence of an association between history of depression and BMD. While users of SSRIs did have a lower mean BMD compared to non-users, the difference was very modest and not statistically significant.

We believe that the null results of our study are likely due to the lack of power, the potential for non-differential misclassification of the exposure, and residual confounding by depression. Our initial power calculations revealed the need of at least 30 users of SSRIs in order to see a mean difference in BMD of 0.1g/cm² between groups. However, only 13 women (5%) reported use of SSRIs, and mean difference of 0.01g/cm² was seen. Increasing the sample size of our population would have led to increased power and perhaps evidence of an inverse association between SSRI use and bone mineral density would have been revealed.

There may have been some non-differential misclassification of the exposure in this study which may have biased our results toward the null. We were limited by the use of self-report questionnaires to determine the exposure, and even further limited by asking only one question concerning SSRI use. Further more; we had no information on dose, duration of use, or reason for use. Information on dose and duration would have allowed us to conduct stratified analysis and assess the temporality of the association.

We did not have the ability to confirm or validate the self-report use of SSRIs in the women. As a result the women may have been incorrectly classified as users or non-users of SSRIs. Finally, if we collected information on reason for use we would have been able to separate the effects of important confounders, most importantly depression, and adjusted accordingly.

The potential effects of residual confounding by depression are outlined below.

X. B. Consistency With Literature

Since this is the first study to examine the relationship between SSRI use and BMD in a young, healthy, and premenopausal women we cannot compare our findings to those of prior studies. However, our study results are consistent with one of the previously published studies examining the relationship between SSRI use and BMD in older postmenopausal women. In their prospective cohort design study, Spangler et al. found no association between SSRI use and 3 year changes in site specific BMD[18] [.003 (-0.0005 to .0069) p=0.09], [.002 (-.0031 to .0078) p=0.40], [.003 (-0.0007 to .0073) p= 0.10] in hip BMD, spine BMD, and total body BMD, respectively, compared with nonusers.

In the study most similar to ours with regards to cross-sectional study design, population size, and premenopausal status, Williams et al.[22] found a lower mean percent of BMD at all sites measured: femoral neck was 5.6% lower, [0.977 (0.116) vs. 0.922 (0.117) p=0.03], trochanter was 6.2% lower, [0.813 (0.105) vs. 0.763 (0.107) p=0.04], and mid forearm was 4.4% lower, [0.745 (0.007) vs. 0.712 (0.068) p=0.03]. In contrast, in our study, we found no evidence of a relationship between SSRI use and bone mineral density or bone mineral content.

X. C. Study Limitations

X. C. 1 Nondifferential Misclassification of Exposure

SSRI use was measured using a self-report questionnaire, administered by a single trained interviewer at one study location, and assessed simultaneously with outcome. The participants answered only a single question related to SSRI use, and were not asked to bring in the prescription bottles or name the specific SSRI used. Some participants may not have known which type of antidepressant they take, and thus misreported SSRI use, or they may not be willing to admit they take any antidepressants due to social stigma. Likewise, some women may have inadvertently answered "yes" to the SSRI question. They may have been using MAOI's or another psychotropic medication not known the difference in the types. This may have lead to nondifferential misclassification of the exposure, or misclassification between users and non-users of SSRI. This misclassification would have biased our results toward the null.

In order to prevent misclassification in this study we asked only about current SSRI use. Current use is easier to recall compared to ever or past use. Even with this restriction it is possible that non-differential misclassification of the exposure occurred, though we expect the impact of the misclassification to be modest.

X. C. 2 Nondifferential Misclassification of the Outcome

The outcomes of the study, BMD and BMC, were measured using total body DEXA scans. DEXA scans are a highly precise method of ascertaining total body BMD and BMC and results are highly correlated with those from site specific DEXA scans.[14] The DEXA scanner used was calibrated daily following manufacturer instructions and all scans were analyzed with the included software. [25] The scans were also performed by two

technicians who did not know the disease or exposure status of the participants. [25] However, it is possible that some imprecision in the DEXA scanner was present and this resulted in inaccurate measures. If this non-differential misclassification did occur then our results would be biased towards the null. However, given the precision of the techniques used in the study to ascertain outcome we believe that the likelihood of nondifferential misclassification of the outcome was low and the impact minimal.

X. C. 3 Confounding

Confounding was accounted for in the study by adjusting for known covariates previously noted in the literature. Because information on potential confounders was collected using self-report questionnaires, we may have some residual confounding in the study. For instance, we collected information on physical activity, which we assessed as a potential confounder of the relationship between SSRI use and BMD. Physical activity was a significant predictor of BMD and BMC in this population. If women who take SSRIs were more likely to have significantly different levels of physical activity compared to the non-users then our results would be overestimated. It is possible that our questionnaire failed to collect accurate information on physical activity leading to a miscalculation of the MET hours/week variable and resulting in residual confounding even after adjusting for it in the model.

Previous studies have hypothesized an association between depression and bone health; therefore we felt it important to consider its role in our study.[5, 15, 22, 23] In addition, depression is inversely associated with BMD through several mechanisms including: vitamin D metabolism, diet, and behavioral factors. We collected information on history of depression from the participants via a self-report questionnaire. After evaluation of

history of depression in our initial models, we found it to be significantly associated with SSRI use however, due to small numbers of women reporting depression and even smaller numbers reporting SSRI use, there was no evidence that history of depression was associated with BMD in our study.

We did not collect information on the reason SSRIs were prescribed. If SSRIs were prescribed for a medical condition independently associated with BMD, such as anorexia nervosa, [16] or depression and if this condition was positively associated with SSRI use then it is possible that not including this as a confounder would overestimate our results. We believe that the impact of this in our study was minimal due to the overall null finding of the study.

X. C. 4 Selection Bias

Selection bias in this study would exist if women with low BMD who take SSRIs were more likely to participate in the study than the participants who used SSRIs and did not have low BMD or those who did not use SSRIs with low BMD or those who did not use SSRIs and did not have low BMD. It is possible that women who are taking SSRIs and have low BMD are more likely to visit their physician, because of these conditions and are therefore more likely to encounter an advertisement for the study. If these women were more likely to enroll in the study then this would result in an overestimation of the SSRI users/low BMD cell. This is selection bias and if it occurred it would lead to an overestimation of the risk. The magnitude of selection bias in our study is likely to be low, due to the rarity of low BMD in this population of women who are at peak BMD and the likelihood that most women are not aware of their BMD.

X. C. 5 Information Bias

One potential source of information bias in our study was surveillance bias. If bone mineral density or bone mineral content was assessed differently between users and non-users of SSRIs then this may lead to information bias. We do not feel that this affected our study due to the accuracy of the DEXA scanner. The technicians administering the scans were both blinded to whether or not the participant used SSRIs. Both were also highly trained in the maintenance and operation of the scanner. However, it is possible that the machine has some error associated with its measurement and reporting of BMD or BMC. This error would have been randomly distributed between the users and non-users of SSRIs.

X. C. 6 Temporal Issues

In this study we are evaluating whether SSRI use was associated with lower BMD; however it may be possible that lower BMD led to SSRI use. Women who have a lower mean BMD may become depressed due to their condition and therefore use SSRIs. We do not believe temporal issues will affect our study because women were likely not aware of their BMD status.

X. C. 7 Survivor Bias

For our study, if those with lower mean BMD who have the highest level of SSRI use are more likely to die of the inverse changes to their BMD due to the level of exposure and if these women die before we can enroll them in the study then the diseased/user cell is decreased and our results would be underestimated. This is highly unlikely in this study because at this age range, a change to BMD or BMC is not fatal.

Most notably, our population of young women has not had enough time to develop severe or life threatening forms of the condition, such as osteopenia or osteoporosis.

X. C. 8 Generalizability

This study is generalizable to women who use the same formulations of SSRIs found in this country. Different formulations of SSRIs found outside the U.S. may not have the same effect on BMD or BMC as the formulation in the U.S. This study may also not be generalizable to men. The physiological mechanism of SSRIs affect BMD or BMC may differ between men and women.

X. D. Study Conclusion

In this study there was no evidence of a statistically significant relationship between SSRI use by young, premenopausal women aged 18-30 and BMD. Because the use of SSRI medications remains high in the general population any potential adverse affects should be examined. Further research should include larger cross-sectional studies and prospective cohort studies. In order to maximize power to examine the relationship it may be necessary to over sample from women with a history of depression.

APPENDIX

TABLES

Table 1: Characteristics of UMass Vitamin D Status Study Population, Selective Serotonin Reuptake Inhibitor Use and Bone Mineral Density g/cm^2,UMass Vitmain D Status Study, 2006-201, N=256

Continuous Variables	**N**	**Mean**	**SD**	**minimum**	**maximum**
Age (years)	254	21.7	4.3	18	69.9
Physical Activity Level (METs/wk)	248	176.6	69.7	63.5	403
Body Mass Index (kg/m^2)	256	23	3.3	16.7	37.8
Calcium Intake (mg/day)	237	1196.1	565.5	128.8	4600.6
Vitamin D Intake (IU/day)	237	380.2	298	3.4	1806.1
Catergorical Variables	**N**	**%**			
Parity					
yes	8	3.1			
no	247	96.9			
Alcohol use					
none/light	135	52.7			
moderate	61	23.8			
heavy	60	23.4			
Current OC use					
yes	109	42.6			
no	147	57.4			
Current Smoker					
yes	15	5.9			
no	240	94.1			
Race					
White	219	85.9			
other	36	14.1			
History of Depression					
yes	33	12.9			
no	223	87.1			
Age at menarche					
<14	202	78.9			
>14	54	21.1			
Calcium (mg/day)					
low	200	78.1			
moderate	53	20.7			
high	3	1.2			
Vitamin D (IU/day)					
low	217	84.8			
moderate	35	13.7			
high	4	1.6			
Vitamin D (IU/day)					
<100	57	22.3			
>100	199	77.7			

Table 2. Distribution of Selective Serotonin Reuptake Inhibitor Use; UMass Vitamin D Status Study, 2006-2011

SSRI use	N	%
Yes	13	5.08
No	243	94.92

Table 3: Distribution of Bone Mineral Density and Bone Mineral Content, UMass Vitamin D Status Study, 2006-2011, N= 246

Bone Measurement	N	Mean	SD	Minimum	Maximum	Missing
aBMD (g/cm²)*	246	1.16	0.08	0.97	1.4	10
BMC (grams)**	246	2541.5	349.2	1833	3682	10

*bone mineral density

**bone mineral content

Table 4: Distribution of Covariates According to Selective Serotonin Reuptake Inhibitor Use: UMass Vitamin D Status Study, 2006-201, N=246

	SSRI Use		
	Yes	No	
Continuous Variables*	**Mean (SD)**	**Mean (SD)**	**P value**
Age (years)	21.6 (3.3)	21.7 (4.3)	0.93
Body Mass Index (kg/m²)	24.9 (5.1)	22.9 (3.2)	0.19
Physical Activity (METs/wk)	156.0 (49.4)	177.7 (70.6)	0.27
Calcium Intake (mg/day)	1166.1 (372.4)	1197.6 (574.5)	0.85
Vitamin D Intake (IU/day)	400.9 (290.2)	379.1 (298.9)	0.81
Categorical Variables	**Yes, N (%)**	**No, N(%)**	**P value****
Parity			0.99
yes	0 (0)	8 (3.1)	
no	13 (5.1)	234 (91.8)	
Alcohol use (g/day)			0.28
none/light	7 (2.7)	128 (50)	
moderate	5 (2.0)	56 (21.9)	
heavy	1 (1.4)	59 (23.1)	
Current OC use			0.47
yes	4 (1.6)	105 (41.0)	
no	9 (3.5)	138 (53.9)	
Current smoker			0.99
yes	0 (0)	15 (5.9)	
no	13 (5.1)	227 (89.0)	
Race			0.7
white	12 (4.7)	207 (81.2)	
other	1 (0.4)	35 (13.7)	
Calcium Intake (mg/day)***			0.78
low	10 (3.9)	190 (74.2)	
moderate	3 (1.2)	50 (19.5)	
high	0 (0)	3 (1.2)	
Vitamin D Intake (IU/day)***			0.51
low	10 (3.9)	207 (80.9)	
moderate	3 (1.2)	32 (12.5)	
high	0 (0)	4 (1.6)	
Vitamin D level (IU/day)			0.74
<100	2(0.8)	55 (21.5)	
>100	11 (4.3)	188 (73.4)	
History of Depression			<0.001
yes	11 (4.3)	22 (8.6)	
no	2 (0.8)	221 (86.3)	
Age at Menarche (years)			0.31
<14	12 (4.7)	190 (74.2)	
>14	1 (0.4)	53 (20.7)	

*two-sided ttest
**Fisher's Exact Test
***Categorical Levels

Table 5: Change in Bone Mineral Density (Beta, SE) in g/cm² Associated with Covariates: UMass Vitamin D Status Study 2006-201, N=246

		BMD			
Continuous Variables*	**β**	**SE**			**P value**
Age (years)	0.0004	0.001			0.72
Body Mass Index (kg/m²)	0.009	0.0014			<.0001
Physical Activity (METs/wk)	0.0002	0.00007			0.0007
Calcium Intake (mg/day)	0.000005	0.000009			0.56
Vitamin D Intake (IU/day)	0.00002	0.0000017			0.22
Categorical Variables*	**Mean (SD)**	**β**	**SE**	**r²**	**P value**
Parity					
yes	1.14 (0.08)	-0.02	0.03	0.003	0.42
no	1.16 (0.08)				
Alcohol use (g/day)					
none/light	1.16 (0.08)	-0.0003	0.006	0.000009	0.13
moderate	1.18 (0.08)				
heavy	1.15 (0.07)				
Current OC use					
yes	1.16 (0.07)	0.007	0.01	0.002	0.51
no	1.16 (0.08)				
Current smoker					
yes	1.16 (0.06)	-0.002	0.02	0.00006	0.9
no	1.16 (0.08)				
Race					
white	1.16 (0.08)	0.01	0.01	0.003	0.43
other	1.17 (0.08)				
Calcium Intake (mg/day)					
low	1.16 (0.08)	0.008	0.01	0.003	0.35
moderate	1.17 (0.08)				
high	1.12 (0.05)				
Vitamin D Intake (IU/day)					
low	1.16 (0.08)	0.016	0.01	0.007	0.29
moderate	1.18 (0.09)				
high	1.16 (0.08)				
Vitamin D level (IU/day)					
<100	1.16 (0.08)	0.004	0.01	0.0005	0.73
>100	1.16 (0.08)				
History of Depression					
yes	1.17 (0.08)	0.02	0.01	0.005	0.29
no	1.16 (0.08)				
Age at Menarche (years)					
<14	1.16 (0.08)	-0.01	0.01	0.005	0.29
>14	1.15 (0.08)				

*one predictor linear regression

Table 6: Change in Bone Mineral Content (Beta, SE) in grams Assoicated With Covariates: UMass Vitamin D Status Study 2006-201, N=246

		BMD			
Continuous Variables*		**β**	**SE**		**P value**
Age (years)		2.15	7.47		0.77
Body Mass Index (kg/m²)		45.62	6.12		<.0001
Physical Activity (METs/wk)		0.8	0.33		0.02
Calcium Intake (mg/day)		0.005	0.04		0.22
Vitamin D Intake (IU/day)		0.07	0.08		0.4
Categorical Variables*	**Mean (sd)**	**β**	**SE**	**r²**	**P value**
Parity					
yes	2457 (428)	-86.57	125.64	0.002	0.49
no	2544 (346)				
Alcohol use (g/day)					
none/light	2533 (368)	-1.39	27.08	0	0.96
moderate	2582 (347)				
heavy	2519 (305)				
Current OC use					
yes	2535 (323)	-10.67	45.15	0.0002	0.81
no	2546 (368)				
Current smoker					
yes	2459 (214)	-88.03	93.05	0.004	0.35
no	2547 (356)				
Race					
white	2541 (336)	4.04	63.86	0	0.94
other	2545 (426)				
Calcium Intake (mg/day)					
low	2519 (334)	0.05	0.04	0.007	0.22
moderate	2622 (399)				
high	2615 (273)				
Vitamin D Intake (IU/day)					
low	2529 (340)	58.13	53.33	0.005	0.28
moderate	2619 (400)				
high	2525 (369)				
Vitamin D level (IU/day)					
<100	2521 (338)	26.08	53.51	0.001	0.63
>100	2547 (353)				
History of Depression					
yes	2600 (361)	67.58	66.17	0.0043	0.31
no	2533 (347)				
Age at Menarche (years)					
<14	2543 (352)	-8.73	55.02	0.0001	0.87
>14	2535 (343)				

* single predictor linear regression

Table 7:Distribution of Bone Mineral Density (g/cm²) and Bone Mineral Content (grams) by level of Selective Serotonin Reuptake Inhibitor Use; UMass Vitamin D Status Study, 2006-2011, N=246

BMD (g/cm²)	SSRI Use	N	Mean	SD	Min	Max	Median	Range
	Yes	12	1.16	0.06	1.07	1.28	1.15	0.21
	No	234	1.17	0.08	0.97	1.38	1.16	0.41
BMC (g)	**SSRI Use**	**N**	**Mean**	**SD**	**Min**	**Max**	**Median**	**Range**
	Yes	12	2549	285	1992	2974	2540	982
	No	234	2541	353	1833	3682	2514	1849

Table 8: Crude and Adjusted Association of Selective Serotonin Reuptake Inhibitor Use and Bone Mineral Density (g/cm²) and Bone Mineral Content (g), UMass Vitamin D Status Study, 2006-2011, N=246

BMD (g/cm²)	Mean (SD)+	Unadjusted β (SE)	P value	Age Adjusted β (SE)	P value	Fully Adjusted β (SE)*	P value
SSRI Use	1.15(0.07)	0.006(0.02)	0.78	0.006 (0.02)	0.78	-0.0094 (0.02)	0.66
SSRI No Use	1.16 (0.07)						
BMC (g)	**Mean (SD)+**	**Unadjusted β (SE)**	**P value**	**Age Adjusted β (SE)**	**P value**	**Fully Adjusted β (SE)***	**P value**
SSRI Use	2467 (316)	8.35 (103.56)	0.94	10.35 (103.63)	0.92	-80.43 (95.03)	0.39
SSRI No Use	2548 (316)						

*adjusted for age, BMI, and physical activity

+Least Squares adjusted for age, bmi, and physical activity

Table 9:Crude and Adjusted Association of History of Depression and Bone Mineral Density (g/cm²) and Bone Mineral Content (grams); Umass Vitamin D Status Study, 2006-2011, N=246

BMD g/cm²	N (%)	Mean (SD)	Min	Max	Median	Range	P value*
History of Depression	33 (12.89)	1.17 (0.08)	1.04	1.36	1.16	0.32	0.29
No History of Depression	223 (87.1)	1.16 (0.08)	0.97	1.38	1.16	0.41	
BMC (g)	**N (%)**	**Mean (SD)**	**Min**	**Max**	**Median**	**Range**	**P value***
History of Depression	33 (12)	2600 (361)	1992	3322	2546	1330	0.31
No History of Depression	223 (87)	2532 (347)	1833	3682	2510	1330	

* Two sided T test

Table 10: Relation of Bone Mineral Density (g/cm²) and Bone Mineral Content (grams) and History of Depression; Umass Vitamin D Status Study, 2006-2011, N=246

	β	SE	r²	Pr(t)
BMD (g/cm²)	0.015	0.015	0.005	0.29
BMC (g)	67.58	66.17	0.0043	0.31

REFERENCES

1. Bertone-Johnson ER, Chocano-Bedoya P. O., Zagarins S. E., et al. Dietary vitamin D intake, 25-hydroxyvitamin D3 levels and premenstrual syndrome in a college-aged population. Journal of Steroid Biochemistry and Molecular Biology. 2010;121: 434, 435-437. (doi: 10.1016/j.jsbmb.2010.03.076).

2. Bliziotes M. M., Eshleman A. J., Zhang X.-W., et al. Neurotransmitter Action in Osteoblasts: Expression of a Functional System for Serotonin Receptor Activation and Reuptake. Bone. 2001; 29(5):477,478-486.

3. Cauley J., Fullman R., Stone K., et al. Factors associated with the lumbar spine and proximal femur bone mineral density in older men. Osteoporosis Int. 2005;16: 1525, 1526-1537.

4. Charney D. S., Nestler E. J., eds. Neurobiology of Mental Illness. 3rd edition ed. New York, NY: Oxford University Press, 2009.

5. Cizza G., Primma S., Csako G. Depression as a Risk Factor for Osteoporosis. J tem. 2009; 20(8):367,368-373. (doi: 10.1016/j.tem.2009.05.003).

6. Diem S. J., Blackwell T. L., Stone K. L., et al. Use of Antidepressants and Rates of Hip Bone Loss in older Women. Arch Intern Med. 2007; 167: 1240, 1241-1245.

7. Haney E. M., Warden S. J. Skeletal effects of serotonin (5-hydroxytryptamine) transporter inhibition: evidence from clinical studies. J musculoskelet Neuronal Interact. 2008;8(2):133,134-145.

8. Haney E. M., Warden S. J., Bliziotes M. M. Effects of seletive serotonin reuptake inhibitors on bone health in adults: Time for recommendations about screening, prevention, and management? Bone. 2009; 46:13, 14-17. (doi: 10.1016/j.bone.2009.07.083).

9. Haney E., Chan B., Diem S., et al. Association of low bone mineral density with selective serotonin reuptake inhibitor use by older men. Arch Intern Med. 2007;167:1246,1247-1251.

10. Harman JS, Edlund MJ, Fortney JC. Trends in antidepressant utilization from 2001-2004. psychiatr serv. 2009;60(5):611,612-616.

11. Kinjo M., Setoguchi S. SS, Solomon D. H. Bone mineral density in subjects using central nervous system-active medications. amjmed. 2005; 118: 1414.e7, 1414.e8-1414.e12. (doi:10.1016/j.amjmed.2005.07.033)

12. Kwon A, Bungay KM, Yu P, et al. Antidepressant use: Concordance between self-report and claims records. Medical Care. 2003; 41(3):368,369-374.

13. Looker AC., Melton J, Harris TB., et al. Prevalence and Trends in Low Femur Bone Density Among Older US Adults: NHANES 2005-2006 Compared With NHANES III. JBMR. 2010; 25(1):64, 65-71. (doi: 10.1359/jbmr.090706).

14. Melton LJ, Looker AC, Shepherd JA, et al. Osteoporosis assessment by whole body region vs. site-specific DXA. Osteoporos int. 2005; 16:1558, 1559-1564. (doi: 10.1007/s00198-005-1871-y).

15. Mezuk B., Eaton W., Golden S. H., et al. Depression, Antidepressants, and Bone Mineral Density in a Population-Based Cohort. J Gerontol A Biol Sci Med Sci. 2008; 63(12):1410,1411-1415.

16. Munoz MT, Argente J. Anorexia nervosa in female adolescents: endocrine and bone mineral density disturbances. eje. 2002; 147: 275, 276-286.

17. Richards J. B., Papaioannou A., Adachi J. D., et al. Effect of Selective Serotonin Reuptake Inhibitors on the Risk of Fractures. Arch Intern Med. 2007; 167: 188,189-194.
18. Spangler L., Scholes D., Brunner R. L., et al. Depressive symptoms, Bone Loss, and Fractures in Postmenopausal Women. J Gen Intern Med. 2008; 23(5): 567,568-574. (doi: 10.1007/s11606-008-0525-0).

19. US Department of Health and Human Services, CDC, National Center for Health Statistics. Depression in the United States Household Population 2005-2006. 7th ed. Pratt LA and Brody DJ, Editors. Hyattsville, MD 20782: US Department of Health and Human Services, CDC, National Center for Health Statistics, 2008.

20. Warden S. J., Bliziotes M. M., Wiren K. M., et al. Neural regulation of bone and the skeletal effects of serotonin (5-hydroxytryptamine). J mce. 2005; 242:1,2-9. (doi: 10.1016/j.mce.2005.06.005).

21. Westbroek I., Van der Plas A., de Rooij K. E., et al. Expression of Serotonin Receptors in Bone. JBC. 2001; 276(31):28961,28962-28968. (doi: 10.1074/jbc.M101824200).

22. Williams L. J., Henry M. J., Berk M., et al. Selective Serotonin Reuptake Inhibitor use and Bone Mineral Density in Women with a History of Depression. International clinical psychopharmacology. 2008;23:84,85-87.

23. Wu Q., Liu J., Gallegos-Orozco J. F., et al. Depression, fracture risk, and bone loss: a meta-analysis of cohort studies. Osteoporosis Int. 2010;21:1627,1628-1635. (doi: 10.1007/s00198-010-1181-x).

24. Wu Q., Magnus J. H., Liu J., et al. Depression and Low Bone Mineral Density: a meta-analysis of epidemiologic studies. Osteoporosis Int. 2009;20:1309,1310-1320. (doi: 10.1007/s00198-009-0918x).

25. Zagarins S. E., Ronnenberg A. G., Gehlbach S. H., et al. The Association between Fat Mass and Bone Mass is removed with adjustment for Factors Related to Body Size. Unpublished.