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Nutrition status, bone mass density, and selective serotonin reuptake inhibitors

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ABSTRACT

The association between selective serotonin reuptake inhibitor (SSRI) use and bone mass density (BMD) has been debated. Inadequate diet, which may occur in depressed individuals prescribed SSRIs is also associated with decreased BMD. This study seeks to determine if SSRI use in adults is associated with lower than average BMD while controlling for nutrition related variables. Further, it investigates whether there are potential interactions between micronutrients and SSRI use on BMD. Adults, 655 with an SSRI prescription ≥180 days and 12,372 non-users, were identified in the 2005–2014 National Health and Nutrition Examination Survey (NHANES) data. Survey respondents were propensity score matched on propensity to have an SSRI prescription and compared on femoral neck BMD t-scores. A sub-analysis within SSRI users was conducted to calculate the odds ratio (OR) of having a low (osteopenia or osteoporosis) BMD t-score given SSRI exposure and inadequate daily micronutrient intake. Inadequate daily micronutrient intake was common; over half of SSRI users and non-users had inadequate calcium, vitamin D, and potassium. SSRI use was associated with an absolute reduction of 0.11 in BMD t-score. Inadequate daily vitamin D intake was associated with lower BMD t-scores in both SSRI users and non-users. The interaction of SSRI use and inadequate daily intake of zinc was also associated with low BMD (OR: 1.11, 95% CI: 1.01–1.23). Patient health may be improved by nutritional education, referral to a dietitian, or by micronutrient monitoring by the prescribing physician.

1. Introduction

Maintaining bone mass density (BMD) prevents osteopenia, osteoporosis, and bone fractures. Fifty-five percent of Americans over the age of fifty have a low or osteoporotic BMD (Johnell and Kanis, 2006). Further, a decrease in BMD of one standard deviation or more is associated with a doubled risk of bone fracture (Klotzbuecher et al., 2000).

Selective serotonin reuptake inhibitors (SSRIs) are a drug class used to treat depression and mood disorders, however their use may result in decreased bone density. Across all age groups in the US, antidepressants rank as the third most common prescription (Health, United States, 2010), and 60% of individuals receiving antidepressant drugs have taken them for two or more years (Pratt et al., 2017). One causative pathway suggested by mice models is that a functional 5-hydroxytryplamine (5-HT) system in bone is potentially weakened when certain prescription drugs, such as SSRIs, change the signals for the use of key micronutrients in bone maintenance, which may, over time, decrease BMD (Warden et al., 2008). Serotonin receptors in human bone cell lines have been identified (Bliziotes, 2010; Tsapakis et al., 2012). Several past studies have found an association between SSRI use among adolescents and lower bone density (Calarge et al., 2017; Feuer et al., 2015), as well as increased fracture risk (Sheu et al., 2015; Gagne et al., 2011; Vestergaard et al., 2006; Wu et al., 2012). However, other studies have not found significant associations between SSRI use and decreased BMD (Ham et al., 2017; Diem et al., 2013; Kinjo et al., 2005; Spangler et al., 2008).

A recent meta-analysis concludes an association between SSRI use and decreased BMD exists (Wu et al., 2012), however authors of all recent reviews noted an inconsistency in the use of control variables, estimated effect size, and risk estimates (Wu et al., 2012; Schwan and

Abbreviations: SSRI, selective serotonin reuptake inhibitor; BMD, bone mass density; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; 5-HT, 5-hydroxytryplamine; DXA, dual-energy X-ray absorptiometry; IOM, Institute of Medicine's; RDA, recommended daily allowance; CDC, Centers for Disease Control and Prevention; 25-OH-VitD, 25-hydroxyvitamin D2 and D3

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Hallberg, 2009; Bruyere and Reginster, 2015; Kumar et al., 2018; Sansone and Sansone, 2012). Past studies often focused on studying a single gender (Diem et al., 2013; Spangler et al., 2008; Cauley et al., 2010; Haney et al., 2007; Rauma et al., 2015; Williams et al., 2008), or age group (e.g. adolescents, seniors) (Calarge et al., 2017; Feuer et al., 2015; Sheu et al., 2015; Cauley et al., 2010; Calarge et al., 2010), or used data sources (e.g. claims data) wherein race, ethnicity, weight, smoking status, and nutrition information on subjects is unavailable or was unutilized, all of which affects generalizability of findings. Indeed, recent reviews have noted a gap in the literature due to missing confounders (Wu et al., 2012; Schwan and Hallberg, 2009; Kumar et al., 2018), with two recent publications (Feuer et al., 2015; Kumar et al., 2018) specifically pointing to the need for future studies to explore the effect of known confounders. Past reviews suggest that features of depression, which SSRIs are prescribed to treat, may cause decreased BMD (Schwan and Hallberg, 2009). For example, poor overall food intake and consumption of fewer nutrient-rich food sources affects bone regrowth and is associated with osteoporosis (Nieves, 2005). Research related to adolescents with eating disorders prescribed SSRIs (Couturier et al., 2013) suggests that diet inadequacy may be more common among SSRI users and may contribute to, or be the cause of, decreased BMD. A study of the relationship between adult SSRI use, diet, and BMD could address gaps in the literature.

This study will make use of a sample representative of the US population from the National Health and Nutrition Examination Survey (NHANES) data. The purpose of this research is to first determine if an association exists between SSRI exposure and BMD in adults represented in the NHANES data who do not self-report anorexic traits. We seek to improve on previous studies by using a large sample size, testing a nationally representative sample, controlling for health and demographic variables, and, critically, by controlling for both total calories and micronutrient variables (B_{12}, calcium, vitamin D, phosphorus, potassium, and zinc). Second, we seek to determine whether consuming less than the Institute of Medicine's (IOM) recommended daily allowance (RDA) level of individual micronutrients while taking an SSRI is associated with lower BMD. Diet, unlike demographic traits, is modifiable. Identification of factors that may also interact with the SSRI drug exposure could provide medical practitioners an opportunity to refer, educate, or counsel patients in a way that promotes bone health during antidepressant treatment.

2. Methods

2.1. Study design and data

The 2005–2006, 2009–2010, and 2013–2014 NHANES cross-sectional data were used in this study. As public, deidentified data, this study was exempt from IRB review. The NHANES annual survey is conducted by the Centers for Disease Control and Prevention (CDC) and is collected and weighted to provide a nationally representative sample. Information on demographics, diet, medical history, and pharmaceutical exposure is collected via in-person interview in a medical examination center (MEC) vehicle. Physical examination included anthropometric measurement, blood draws, and referral to a certified radiology technologist for relevant x-rays.

2.2. Inclusion and exclusion criteria

Included NHANES participants are those who participated in the Dual-Energy X-ray Absorptiometry (DXA) femur-neck BMD test and responded in full to the demographic, pharmaceutical, and dietary surveys. Excluded participants were those who had invalid or missing demographic information, dietary and caloric intake values, incomplete femur DXA BMD test results, or who reported taking more than one SSRI at a time. Some SSRIs are prescribed to treat eating disorders, therefore participants with a BMI of $\leq 17.5\,kg/m^2$, an underweight threshold that may indicate anorexia (Fitzpatrick and Lock, 2011), were also excluded.

To be coded as an SSRI user, participants must have reported use for ≥ 180 days. This length of exposure has been previously used (Feuer et al., 2015) and was selected to account for potential changes between medication types and the titration period. Non-users were those defined as individuals reporting no prescription for SSRIs.

2.3. Dependent variable

We investigated BMD (gm/cm^2) from DXA tests on the femur neck of adults. This is the standard of practice for assessing BMD as the test is a noninvasive procedure, affordable, and reliable (Heymsfield et al., 1989). The DXA test determines BMD by the amount of beam absorption that occurs at the region being X-rayed. Studies have shown the DXA can detect total body bone mass changes from a single region X-ray, making it the preferred method of assessment over others, such as histomorphometry as it requires less exposure to radiation (Genant et al., 1996). All tests were administered by certified radiology professionals on informed and consenting NHANES volunteers. The inclusion criteria was adults, non-pregnant, non-allergic to radiographic contrast material, individuals who had not been exposed to radiographic contrast material or nuclear medicine within the previous week, and those weighing < 300 pounds. Scanning was completed with quality-control standards of the University of California at San Francisco's (UCSF) NHANES protocol and Hologic Apex software, version 4.0, was used to analyze femur neck scans on the left hip unless the participant had a personal objection or medical reason for declining a left hip scan (NCHS, 2014).

The femoral neck scores from the DXA scan were compared to that of a healthy 30-year old adult and reported as a t-score (t-score = (participant BMD − reference BMD)/standard deviation of reference), per the World Health Organization's (WHO) standards and recommendations (World Health Organization, 1994; Looker et al., 2012). The American adult reference population used for mean and standard deviation is derived from the CDC's NHANES III data for a healthy 30-year old (Looker et al., 2012; Kelly, 1990). The NHANES III data was produced via a similar study protocol, however it does not include individuals from the 2005–2014 sample used in this study.

The threshold (NIH, 2017) for a normal BMD t-score is ≥ -1, while osteopenia is defined as scores between -1 and -2.5, and osteoporosis is defined as scores ≤ -2.5.

2.4. SSRI usage

Participants were asked to report all pharmaceuticals, by brand name, they had used within the last 30-days. Surveyors provided a visual inspection of prescription bottles, if available, to confirm drug type and drug class. The length of time SSRI prescriptions had been in place was also verified and recorded.

2.5. Demographic variables

Participants disclosed their gender (female or male), race and ethnicity (Caucasian, African American, Hispanic, or other/mixed), household annual income, and education level (less than high school, high school diploma, some college or associates of arts (AA) degree, college degree or above). The categorical education variable was used to create an additional binary variable indicating a participant had at least a high school education, or not.

Age (years) and poverty level were recorded as continuous variables. Poverty level was calculated as the ratio of household income to national poverty level.