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Depression and Osteoporosis: A Research Synthesis with Meta-Analysis

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Abstract

Major depressive disorder has been associated with low bone mineral density. The strength of this association, however, varies greatly among studies; the direction of the causative link is still controversial, and the etiology remains unclear. We aimed to confirm this association, assess its magnitude and estimate its clinical relevancy. A total of 535 articles were initially identified and the research synthesis was based on 33 qualified articles. Of these, 25 articles (or 76 %) showed an inverse relationship between major depression or minor depression or depressive symptoms and bone mineral density or bone turnover. Meta-analysis could be performed on 20 of the initially selected 33 articles. Standardized weighted differences in mean AP spine, total femur and femoral neck bone mineral density, each from at least 10 studies, were computed in g/cm² and transformed into percent differences. At each site, bone mass was lower in subjects with depression as compared to controls: AP spine bone mineral density was 4.73 % lower (95 % CI –7.28 % to –2.19 %, $p < 0.0001$; $n = 16$ studies), total femur bone mineral density was 3.53 % lower (95 % CI –5.66 % to –1.41 %, $p < 0.001$; $n = 13$ studies), and femoral neck bone mineral density was 7.32 % lower (95 % CI –10.67 % to –3.96 %, $p < 0.0005$; $n = 8$ studies). In conclusion, major depressive disorder was associated with lower bone mineral density at the AP spine, femoral neck, and total femur. The deficits in bone mineral density in subjects with depression are of clinical significance and likely to increase fracture risk over the lifetime of these subjects.

Keywords

bone; fractures; stress; antidepressants; women; evidence-based medicine; leptin

Introduction

It is increasingly clear that a bidirectional link exists between major depressive disorders (MDDs), several other mood disorders, and various medical conditions, such as osteoporosis and cardiovascular disease [1]. In 2001, we published the first meta-analysis on the relationship between MDDs and osteoporosis [2]. In spite of growing evidence, however, neither depressive symptoms nor MDDs currently appear among the risk factors for osteoporosis in official statements [3]. In the last NIH consensus conference on osteoporosis, depression was not listed as a risk factor for osteoporosis. A 2006 issue of

Endocrine News, an official publication of the U.S. Endocrine Society, contained an exhaustive table listing 19 causes of secondary osteoporosis, including bone loss secondary to space flight in astronauts, but failed to mention depression for secondary osteoporosis! [4]. The sustained need to change this incorrect, long-standing perception has prompted us to perform another meta-analysis of published studies regarding bone mass in subjects with depression. The main hypothesis tested in this meta-analysis was whether subjects suffering from depression have lower bone mineral density (BMD) than controls. Furthermore, we examined whether the use of different diagnostic criteria for depression and/or clinical severity, duration, and number of depressive episodes may have any effect on the relationship between depression and bone mass. In the studies considered eligible for our meta-analysis, depression was often defined according to the DSM IV criteria, whereas some of the studies explored the potential association between osteoporosis and depressive symptomatology, defined as an aggregate of symptoms that may or may not have met all the DSM criteria for MDDs.

Contextually to the meta-analysis, we performed a research synthesis on the same topic. We felt that this integrated approach would capture the essence of the problem better than either approach alone. In the last 2–3 years there has been a rising trend in the literature of combining meta-analysis with research synthesis. The potential advantages of this novel approach have not been formally tested.

Materials and Methods

Study identification and retrieval

The PubMed, Embase, Biological Abstracts, PsycInfo, Web of Science, and PASCAL electronic databases were searched by experienced librarians from their inception to December 2007 for relevant human studies. Search terms included depression; depressive disorders; osteoporosis; osteopenia; bone density; bone mineral density; dual energy X-ray absorptiometry; DEXA; and DXA. No language restriction was imposed on the search. Two authors (GC and MC) examined each title generated from the search and identified the most relevant articles for which abstracts were obtained.

Study eligibility criteria

To be eligible for the meta-analysis, the study: a) had to be conducted in subjects with major or minor depression, or depressive symptoms along with a group of appropriate controls; b) should contain BMD data in an extractable form; and c) should be published before December 31, 2007 [5–24]. Studies that did not meet the above criteria but were still deemed to be relevant to the present article were part of the research synthesis [25–37].

Data collection

Two authors (GC and MC) extracted, using ad hoc developed forms, the following information from each article eligible for meta-analysis: author, year and journal of publication, sample size, gender, age, menopausal state, characterization of depression, presence of bone mass measurements, and main findings.

Author contact

In cases of incomplete data, authors were contacted whenever possible. Using up to two electronic mail contacts to the corresponding and/or first author of each eligible article, we requested missing data on BMD. All authors who were contacted replied.

Meta-analysis

Meta-analysis was performed with the Comprehensive Meta-analysis software (Biostat™, Englewood, NJ, USA) using the random effects model, a more conservative approach than the fixed effects model [38]. Standardized differences were plotted in mean BMD (expressed in g/cm^2) with 95 % confidence intervals (CIs) between subjects with MDDs and controls. Weighted mean differences and the associated standard deviations (SDs) of BMD values were transformed into percent differences by using the control population as a reference.

We analyzed the difference in BMD between subjects with depression and controls at the AP spine, total femur, and femoral neck. We also compared studies that used a diagnosis of depression based on DSM III or IV criteria (according to the *Diagnostic and Statistical Manual of Mental Disorders*) versus studies that used a diagnosis of depression based on other criteria. Additionally, a meta-analysis of studies with exclusively male populations was performed to evaluate whether depression is associated with low BMD in men as well. The potential for publication bias was examined by constructing a funnel plot, in which effect size of each study was plotted against the standard error. For each study we determined the relative weight. Evidence of heterogeneity across studies was examined by using the I^2 test [39]. To explain reasons for large differences in the effect size between studies (heterogeneity), a priori hypotheses were developed relating to the methodological quality of the study and the study population: (a) different methodologies for diagnosis of depression (DSM vs. other criteria) and (b) gender interaction with BMD. The criterion required for significance, alpha, was set at 0.05. In addition, classical fail-safe n values, that is, the estimated number of studies that in theory would make the p -value greater than alpha, were calculated for each of these three skeletal sites.

Results

The electronic search initially revealed a total of 535 entries in the databases, of which 33 original articles were found to be eligible for assessing the relationship between depression and osteoporosis, based on analysis of the abstract. Fig. 1 describes the flow of candidates and eligible articles for meta-analysis and research synthesis. Twenty articles were suitable for meta-analysis and are summarized in Table 1 [5–24]. Of these, 16 articles contained AP spine data [5, 7–12, 14, 15, 17, 18, 20–24], 13 articles contained BMD total femur data [6–8, 10–11, 13–15, 17–21], and 10 articles assessed BMD at the femoral neck [5, 7, 8, 12, 15–18, 20, 23]. Sites with too few articles available for BMD assessment (5 articles for Ward triangle [8, 17, 18, 21, 23], 5 articles for trochanter [8, 17, 18, 21, 23], and 2 articles for radius [7, 23]) were not used for meta-analysis. Thirteen original articles that could not be included in the meta-analyses as they were published after the cutoff date of December 2007 [25, 26] or did not have BMD data in an extractable form [27–37] are summarized in Table 2.

In principle, the best way to address the question of causality between depression and osteoporosis would be to disprove that treating depression has effects on bone mass (i.e., accepting the null hypothesis). Thus, subjects never treated with depression would be randomized to antidepressants or placebo and followed over time with serial measurements of BMD. Obviously this approach is neither ethical nor feasible. It is therefore not surprising that the studies identified for detailed assessment were all observational in nature. We did evaluate every article for quality and made general comments across the manuscript. We, however, did not use a formal quality scoring system, as these systems are usually applicable only to randomized controlled trials [40] and the articles reviewed here were mostly cross-sectional or prospective natural history studies.

Research synthesis: characteristics of studies identified by literature search for assessing a relationship between depression and osteoporosis

Sample size—With regard to sample size, the available studies could be broadly categorized into 2 different kinds. The larger studies ($n = 13$; $n_{\text{meta}} = 6$) had more than 500 subjects in total, typically with several hundred depressed subjects and up to several thousand controls and were usually population-based studies of BMD or fractures or clinical trials of osteoporosis [6, 11, 13, 15, 19, 21, 27–30, 32, 34, 36]. These studies measured relatively few parameters. The remaining studies ($n = 20$; $n_{\text{meta}} = 14$) were smaller in size and usually clinical series of 100 subjects or less, conducted in patient populations with mood disorders [5, 7–10, 12, 14, 16–18, 20, 22–26, 31, 33, 35, 37]. Generally these studies measured larger numbers of biological parameters.

Gender/menopausal state—Consistent with the epidemiology of both depression and osteoporosis, the majority of studies ($n = 21$; $n_{\text{meta}} = 12$) included only women [5–9, 12, 14, 17, 18, 20, 21, 23, 25–27, 29–33, 35] and 10 studies ($n_{\text{meta}} = 6$) included both genders [10, 13, 16, 19, 22, 24, 28, 34, 36, 37]. Only 2 studies focused on men: one on Chinese men ($n_{\text{meta}} = 1$) [11] and another on white men ($n_{\text{meta}} = 1$) [15]. Women were all premenopausal in 13 studies ($n_{\text{meta}} = 9$) [5, 7, 9, 10, 12–14, 17, 18, 25, 26, 31, 35], all perimenopausal in 1 study ($n_{\text{meta}} = 1$) [8], all postmenopausal in 14 studies ($n_{\text{meta}} = 6$) [6, 16, 19–21, 24, 27–30, 32–34, 37], and 3 studies ($n_{\text{meta}} = 2$) enrolled both pre- and postmenopausal women [22, 23, 36].

Age—Two studies ($n_{\text{meta}} = 1$) were conducted in pediatric populations [9, 25]. In 15 studies ($n_{\text{meta}} = 12$), the mean age of the participants was between 18 and 55 years [5, 7, 8, 10, 12–14, 17, 18, 22–24, 26, 31, 35, 37] and in 13 studies ($n_{\text{meta}} = 6$) the mean age of the population was greater than 55 years [6, 11, 15, 16, 19, 21, 27–30, 32, 34]. Three studies ($n_{\text{meta}} = 1$) overlapped the age categories, defined above [20, 33, 36].

Recruitment—Twelve studies had population-based cohorts ($n_{\text{meta}} = 7$) [6–8, 11, 15, 19, 21, 25, 27, 28, 30, 32], 2 studies had probability samples ($n_{\text{meta}} = 1$) [13, 36], 15 studies were conducted in subjects seeking psychiatric care ($n_{\text{meta}} = 11$) [5, 9, 10, 12, 14, 16–18, 22–24, 26, 31, 35, 37] and only 3 studies ($n_{\text{meta}} = 1$) involved subjects seeking medical attention for osteoporosis [20, 29, 33]. For a remaining study ($n_{\text{meta}} = 0$), the recruitment could not be determined [34].

Geographic location—Twelve studies represented populations from the United States ($n_{\text{meta}} = 8$) [6, 7, 13, 15, 19, 21–23, 25, 27, 30, 36], 11 studies were conducted in Europe ($n_{\text{meta}} = 5$) [9, 14, 16, 20, 24, 26, 31–33, 35, 37], 6 studies ($n_{\text{meta}} = 5$) were conducted in the Middle East [5, 10, 12, 17, 18, 34], 2 studies ($n_{\text{meta}} = 1$) in the Far East [11, 28], 1 in Australia ($n_{\text{meta}} = 1$) [8], and 1 clinical trial ($n_{\text{meta}} = 0$) was international [29].

Diagnostic criteria for depression—Close to half of the studies ($n = 16$, $n_{\text{meta}} = 12$) used DSM III or IV criteria for the diagnosis of depressive disorder [5, 7, 8, 10, 12–14, 17, 18, 22–24, 26, 31, 35, 37]; 9 studies ($n_{\text{meta}} = 4$) used the Geriatric Depression Scale (GDS) – a 15-item self-report validated scale consisting of 15 yes or no questions regarding symptoms of depression experienced in the previous week [6, 11, 15, 21, 27–29, 32, 34]; 2 studies ($n_{\text{meta}} = 1$) used the Center for Epidemiology Studies Depression Scale (CES-D) – a 20-item scale of symptoms over the preceding week [19, 30]; 1 study ($n_{\text{meta}} = 1$) used the General Health Questionnaire – a 28-item self-rating questionnaire covering depression, anxiety, somatic factors and physical dysfunctions [20]; 1 study ($n_{\text{meta}} = 1$) on anorexic girls used the Montgomery-Asberg Depression Scale and the Hamilton depression scale [9]; 1 study ($n_{\text{meta}} = 1$) used Cornell's Scale [16]; 1 study ($n_{\text{meta}} = 0$) used the Children's

Depression Inventory – a 27-item self-reported measure [25]; and another one ($n_{\text{meta}} = 0$) used the General Well Being Schedule (GWB-S) [36]; the remaining study ($n_{\text{meta}} = 0$) used the Zung depression scale – a self-reported scale [33].

Research synthesis: assessment of an association between depression and osteoporosis

Effect of depression on BMD—The original study in 1994 by Schweiger [24] reporting a large (15 %) deficit in spine bone mass by CT in patients with major depression has been followed by a growing number of reports assessing an association between osteoporosis and depression [5–23, 25–37]. Out of a total of 33 relevant articles, 25 (or 76 %) showed an inverse relationship between depression and BMD or bone turnover [5–9, 11, 14, 16, 17, 19, 23–37]. As many of these studies have already been described in detail in a previous review article [2], we provide in this review only highlights and focus on potential mechanisms, clinical consequences, and future research questions.

Osteoporotic fractures in subjects with depression—From a public health point of view, it would be critical to determine whether lower bone mass in subjects with depression translates into increased fracture risk. Bone mineral density is an accepted predictor of osteoporotic fractures; however, it does not account for additional factors involved in fracture risk, such as biomechanical bone strength and anatomical properties [41].

Because of the large sample size and the need for long follow-up, very few studies have addressed the question of fracture prevalence in subjects with depression. While depressive symptoms were more common in women with prevalent vertebral fractures in a prospective study, the direction of the causal link (i. e., whether depression in this study was related to fractures or was caused by osteoporosis) was unclear [29]. In a large study on older Mexican-American women, higher levels of depression were predictive of new fractures, suggesting that depression is a true causative factor for fractures [30].

A prospective, population-based study in Norway found that, after adjustment for other known risk factors for osteoporosis, women with the highest level of mental distress were at greater risk for femur fracture (relative risk, 1.95) [42]. Likewise, data from the NHANES I study showed that, after adjusting for age, gender, race, BMI, smoking, alcohol, and physical activity, depressive symptomatology remained predictive of femur fracture with a hazard ratio (HR) of 1.7 (95 % CI: 0.99–2.91) [36]. In addition, in multiple adjusted models, an association between elevated urinary free cortisol (UFC) and subsequent bone fractures was seen in a cohort of generally healthy older subjects [43].

In the Tromso study, a longitudinal cohort study conducted in Norway, women with depression had an adjusted odds ratio (OR) of 2.5 (95 % CI: 1.3–4.9) for sustaining a nonvertebral fracture, and an OR of 3.1 (95 % CI: 1.3–7.2) for an osteoporotic fracture (femur, pelvis, proximal humerus, and wrist/forearm) [44, 45]. However, similar associations were not found in men. Whooley et al. [21] reported that women with depression had a 40 % increased risk for sustaining a nonvertebral fracture compared to women without depression. This association remained strong even after adjusting for various confounding factors and for the increased propensity to falls among women with depression. In this study, the OR for a vertebral fracture was 2.3 (95 % CI 1.6 – 3.2) among women with depression. Interestingly, no significant differences were found in the spine or femur BMD between depressed women and controls in this study.

Evidence for an association between depression and osteoporosis: results of the meta-analyses

Twenty articles with control groups for meta-analysis are summarized in Table 1 [5–24]. The primary outcome for meta-analysis was the difference in BMD between subjects with MDD and nondepressed controls at the 3 skeletal sites for which there were sufficient number of articles (arbitrarily defined as 10 or more). A number of articles reported BMD data for various skeletal sites: AP spine 16 [5, 7–12, 14, 15, 17, 18, 20–24], total femur/hip 13 [6–8, 10, 11, 13–15, 17–21], femoral neck 9 [5, 7, 8, 12, 16–18, 20, 23], trochanter 5 [8, 17, 18, 21, 23], Ward triangle 5 [8, 17, 18, 21, 23], and radius 2 [7, 23]. Of note is that, because many articles reported more than one extractable study by bone site, gender, or menopausal state, the number of studies used for meta-analysis is often higher than the number of articles.

Measurement of BMD and adjustment for confounding factors in subjects with depression

Apart from the very first study reporting an association between depression and osteoporosis [24] that used quantitative CT, all other studies in this meta-analysis involved the use of DXA scanning for BMD measurements. Bone mineral density values adjusted for factors known to affect BMD were extractable only from 4 articles [8, 13, 15, 21]. In 2 articles adjustments had been made, but only the unadjusted BMD values were reported [9, 24].

Bone mineral density at AP spine

According to meta-analysis of 18 studies on AP spine BMD data from 16 articles [5, 7–12, 14, 15, 17, 18, 20–24], subjects with depression had 4.73 % lower bone mass (95 % CI: –7.28 to –2.19 %, $p < 0.0005$) than controls (Fig. 2). The classical fail-safe, defined as the number of nonsignificant studies that would be necessary to reduce the effect size to an nonsignificant value, defined in this study as an effect size of 0.05 was quite large totaling 228 (Table 3), making highly unlikely that the conclusion were the result of publication bias. The deficit in bone mass compared to controls was more accentuated in the 11 reports [5, 7, 8, 10, 12, 14, 17, 18, 22–24] that used DSM criteria to diagnose depression (–4.68 %; 95 % CI: –7.81, –1.44; $p < 0.004$ vs. controls) than in the remaining 5 reports [9, 11, 15, 20, 21] that used non-DSM criteria to diagnose depression (–2.27 %; 95 % CI: –4.41 to –0.14; $p < 0.04$ vs. controls).

Bone mineral density at total femur

Meta-analysis of 15 studies [6–8, 10, 11, 13–15, 17–21] on BMD at the total femur from 13 articles showed that subjects with depression have 3.53 % lower bone mass than controls (95 % CI: –5.66 % to –1.41 %, $p < 0.001$) (Fig. 2) with the classical “failsafe n ” equal to 133 studies (Table 3). At this site, the deficit in bone mass was similar in the 7 reports [7, 8, 10, 13, 14, 17, 18] using DSM criteria (–2.69 %; 95 % CI: –5.38 to 0.004; $p < 0.005$) and in the 6 reports [6, 11, 15, 19–21] using other criteria to diagnose depression (–2.37; 95 % CI: –4.69 to –0.044; $p < 0.046$).

Bone mineral density at femoral neck

Based on 8 studies [5, 7, 12, 16–18, 20, 23] on bone mass at the femoral neck from 8 articles, subjects with depression had a 7.32 % lower bone mass than controls (Fig. 2), with the classical “fail-safe n ” equal to 130 studies (Table 3). Compared to the AP spine and the total femur (see above) this site revealed the greatest deficit in subject with depression versus controls (–7.32 %; 95 % CI: –10.67 to –3.96; $p < 0.0005$). Also of note is that 6 out of these 8 studies used DSM criteria for the diagnosis of depression [5, 7, 12, 17, 18, 23].

Gender differences in BMD

At the AP spine, the deficit in bone mass was significant in women with depression (-5.57% ; 95 % CI: -8.51 to -2.64 ; $p < 0.0005$) [5, 7–10, 12, 14, 17, 18, 20, 21, 23, 24] but not in men with depression (-1.50% ; 95 % CI: -4.28 to 1.28 ; $p < 0.29$) [10, 11, 15, 24]. At the total femur, the deficit in bone mass was evident in both genders and was of similar magnitude (women: -3.89% ; 95 % CI: -6.85 to -0.93 ; $p < 0.01$ [6–8, 10, 13, 14, 17–21]; men: -3.27% ; 95 % CI 5.34 to -1.19 ; $p < 0.002$; [10, 11, 13, 15]). There were not enough studies to perform a formal analysis at the femoral neck of bone mass in men.

Differences in osteocalcin levels

Osteocalcin is a biomarker of bone formation and 8 articles reported on osteocalcin levels [5, 7, 12, 17, 18, 23, 31, 35]. According to meta-analysis of the 6 articles with extractable data [5, 7, 12, 17, 18, 23], there were no differences in osteocalcin levels between subjects with depression and controls (-7.65% ; 95 % CI: -21.23 to 5.93 ; $p < 0.27$).

Qualitative global assessment of the studies reviewed

A large proportion of the studies reviewed (25/33) reported an association between depression and low BMD (Table 3). An examination of the 8 remaining studies that confirmed the “null hypothesis” (i. e., no association between depression and osteoporosis) failed to reveal any specific pattern in reference to the age of the study sample, size, menopausal status, or geographic location.

Discussion

The results of this research synthesis with meta-analysis prove that MDDs are associated with low bone mass and should therefore be considered a risk factor for osteoporosis (Table 3). According to our meta-analysis, BMD in subjects with MDDs was 4.7 % lower at the AP spine, 3.5 % lower at the total femur, and 7.3 % lower at the femoral neck as compared to healthy controls. These differences translate to an approximate 1 SD deficit in spine and 0.6 SD in total femur and are similar or greater than those produced by recognized risk factors for osteoporosis, including life style factors. For example, smoking is associated with an approximately 0.1 SD deficit in BMD for combined skeletal sites [46], lack of exercise (aerobics and weight bearing) with a 0.3 SD deficit in the spine and 0.1 SD deficit in the femur [47], and absence of calcium supplementation with a 0.4 SD deficit in whole body BMD [48].

BMD is a strong predictor of fracture risk. Large, prospective studies conducted mostly in postmenopausal women showed that the absolute risk for fractures increases with increasing age for the same level of BMD. As an example, the NORA study convincingly demonstrated that for a T score of -2.0 to -1.0 there is a four-fold increase in the risk for femur and vertebral fractures in women aged 70 to 79 compared to women aged 50 to 59 [49]. Therefore, the percent loss in BMD observed in subjects with depression likely translates to increasing fracture risk with age, even in the absence of further bone loss. Of note is that the largest deficit in bone mass was observed at the femoral neck in subjects with depression. This important finding makes depression-related osteoporosis a particularly serious medical problem, since femur fractures are far more serious than fractures at other skeletal sites.

The 6 studies available for assessment detected no difference in osteocalcin levels between subjects with depression and controls. More information on changes in biochemical markers of bone turnover is needed to clarify whether the bone deficit in depression is caused by increased bone resorption, decreased bone formation, or both. Such information could guide pharmacological treatments for osteoporosis in this population. In a recently published meta-

analysis of 14 studies on the same topic, Wu et al. [50] found a similar relationship of BMD and depression after pooling together skeletal sites into two regions: femur and spine. In the present meta-analysis of 20 studies, we determined the effects of depression on BMD at the AP spine, the total femur, and the femoral neck. In another recent meta-analysis, Yirmia et al. [51] found a similar relationship between depression and decreased BMD; in their study they did not, however, perform subanalyses of males, females and mixed populations as we did here. In addition, unlike Wu et al. [50] and Yirmia et al. [51], we report the effects of depression on BMD in percent differences, a value that is clinically more meaningful and intuitive than the absolute difference in BMD or the effect size. Despite an earlier cutoff date, our meta-analysis includes more studies, with data from a greater number of depressed subjects than the two recently published articles [50, 51].

Potential mechanisms of bone loss in depression

Several endocrine alterations observed during the depressive state may induce bone loss [52]. Depression is associated with alterations of the hypothalamic-pituitary-adrenal (HPA) axis at multiple levels, including altered secretion of hypothalamic corticotropin-releasing hormone (CRH), as indicated by CRH levels in the cerebrospinal fluid, and change in the set point threshold for negative feedback; these changes generally result into hyper-cortisolism, as recently reviewed [52]. In an animal model, increased sympathetic tone induced via chronic and severe stress caused bone loss [53]. Evidence in humans is scanty but a recent survey conducted in Israel reported an association between generalized anxiety disorder and osteoporosis [54]. A secular trend to increased psychosocial stress has been reported which may be contributing to the obesity epidemics as well [55]. Although alterations in leptin levels, often of opposite sign, have been reported in subjects with depression, the effects of hyper-leptinemia on bone mass in humans are not clear [52]. In the *ob/ob* mouse, a genetic model of leptin deficiency, intracerebro-ventricular leptin administration causes bone loss by inhibiting bone formation [52]. Proinflammatory cytokines are increased in depression and IL-6 is a potent activator of the osteoclast [52]. Both estrogen deficiency in women and androgen deficiency in men may affect bone mass and there is at least theoretical evidence for decreased sexual hormones in both genders during the acute phases of depression. Serotonin transporter receptors are present on the osteoblast and use of antidepressants has been associated with more fractures [52]. Commonly accepted life style risk factors for osteoporosis include smoking, inadequate calcium intake, excessive alcohol intake, and physical inactivity. Although in theory these factors may all contribute to bone loss in subjects with depression [52] at the present time, there is little evidence from studies of depressed subjects that poor lifestyle was more prevalent in subjects with depression than controls.

Recently, an unexpected link between bone and energy metabolism has been reported: physiological amounts of osteocalcin increase the expression of insulin in the pancreatic beta cell, increase glucose utilization in muscle and other peripheral tissues, and stimulate the production of adiponectin by the adipocyte [56]. Major depressive disorders are known to increase the risk for type II diabetes with an hazard ratio of 1.62, an effect that does not appear to be mediated by poor health behaviors [57] and osteocalcin levels are inversely related to metabolic syndrome [58] and diabetes [59]. Further studies are warranted in subjects with depression to investigate the clinical implications of these novel pathways linking bone and energy metabolism.

Study Limitations

The studies included in our meta-analysis had several limitations. There was a significant heterogeneity among the various studies in terms of differences in BMD that was most likely real, rather than attributable to measurement error. In the case of DXA, the error is

remarkably small (about 1 %). Even after removing the most extreme studies from the meta-analysis for AP spine and total femur, a significant amount of heterogeneity remained (with I^2 above 60 %). Possible reasons for the heterogeneity include: a) Differences in methodology. All articles had a cross-sectional design, but some were case series collected prospectively mostly for reasons different from observing the natural history of bone turn-over in depression, whereas others represented retrospective analyses. b) Differences in the diagnosis and definition of depression. As an example, the DSM criteria for depression have evolved over time and were used inconsistently in various studies. c) Differences in age, gender, sample size, geographic location, and use of antidepressant medication among study populations. d) Differences in adjustment for known osteoporosis risk factors (Fig. 3).

Conclusions

Implications for practice

The results of this research synthesis with meta-analysis confirm that major depressive disorder is an important but still unrecognized risk factor for osteoporosis. Premenopausal women with major depression should undergo DXA screening. A similar recommendation may be made for postmenopausal women with depression, especially in the presence of one or more known risk factors for osteoporosis. More studies on bone turn-over are needed in men with major depression, before being able to make specific recommendations about screening by DXA. In addition, given the cost and the fact that DXA involves use of radiation, albeit limited, carefully designed studies of health economics should establish the cost/benefit of large scale screenings. Once a diagnosis of osteoporosis is made in subjects with major depression, DXA measurements should be performed with a frequency based on the current WHO algorithm; this model takes into account the presence of other risk factors and the age of the subjects [60]. As far as the diagnosis of depression is concerned, it is well known that this condition may easily go undiagnosed especially in a primary care setting, and that physicians' recognition of depression is relatively poor, approximately 30–50 % [62]. Several self-reported screening questionnaires are available that perform quite well and take little time; therefore, we recommend screening tools for depression in any setting (medical orthopedic, ob/gyn) in which a subject with decreased BMD or a nontraumatic fracture may present [62].

Implications for research

Since most of the available evidence comes from cross-sectional studies, we advocate longitudinal controlled studies of BMD and bone turnover to establish causality. Data on fractures in subjects with depression are limited; it would therefore be interesting to see whether fracture risk in subjects with depression is totally accounted for by changes in BMD or whether use of medications, alterations in balance, and other unknown factors may play an additional role. It is important to conclusively establish the potential effect of antidepressant medications on the bone mass. Irrespective of the study on specific population of subjects with depression, studies on bone turnover are needed in men and women with depression. As there is biological evidence to suggest that subjects with post-traumatic stress disorder (PTSD) may be at increased risk for osteoporosis, this question should be further explored with clinical studies. In light of the recent developments in the endocrinology of the adipose tissue [63], the role of leptin on bone mass and changes in osteocalcin levels on energy metabolism in subjects with depression should be examined. Although it is commonly accepted that both depression and osteoporosis have a clear genetic component, the search for a genetic background common to these two conditions remains elusive. Identical twin studies examining the lifetime association between depression and osteoporosis may help shed light on the role played by genetic versus environmental factors in the comorbidity of these two conditions.

Glossary of Terms

A forest plot	is a graphical display of the results of a meta-analysis.
The relative weight	of each individual study is a critical information that allows more emphasis (weight) to be given to larger studies, as smaller studies may be more subjected to chance and sampling bias. This method allows avoidance of bias inherent in mere arithmetical average of each individual study result.
The funnel plot	is used primarily to provide a visual aid to detect bias or systematic heterogeneity. In the absence of bias, a symmetrical inverted scatterplot derived by plotting treatment effect (in this particular case the standardized differences in bone mineral density) against a measure of study size (in this case the standard error of bone mineral density). Of note, larger studies tend to have a smaller standard error, as a result of greater precision and to aggregate towards the vertex of the triangle.

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Fig. 1.
Disposition diagram for bone density/depression studies.

Fig. 2.

Meta-analysis forest plots for AP spine BMD, total femur BMD, and femoral neck BMD. **a** : AP spine BMD: Most studies show lower AP spine BMD in depressed subjects, with 3 studies indicating that BMD was higher in controls. **b** : Total femur: Most studies show lower total femur BMD in depressed subjects, with 3 studies indicating that BMD was higher in controls, and 2 studies showing no difference. **c** : Femoral neck BMD: Most studies show lower femoral neck BMD in depressed subjects, with 3 studies indicating that BMD was higher in controls. Note: although reportedly measured, no data were provided for the femoral neck in reference [8]. For each one of these 3 graphs under the first column are listed in chronological order the studies included and the year of publication; these studies are subdivided in studies conducted only in women, only in men, and studies conducted in men and women. Studies that utilized DSM criteria to characterize depression are indicated with a dagger. In the last column the relative weight of each individual study is reported.

Fig. 3.

Funnel plots for AP spine BMD, total femur BMD and femoral neck. **a:** AP Spine BMD: Funnel plot shows slight asymmetry with several outliers, which may be due to different effect sizes of depression in men and women, or depression treatment effects. To further analyze publication bias, we computed the estimated number of studies that in theory would bring p-value to a number greater than alpha. For AP spine that number is 228, giving more weight to the results despite the presence of several outliers on the funnel plot. **b:** Total femur BMD: Funnel plot is fairly symmetrical, but several outliers were still present. In this case, the number of studies that would bring p-value to a number greater than alpha is 133. **c:** Femoral neck: Funnel plot shows slight asymmetry with several significant outliers. This, however, may be simply accounted by the small number of studies that reported on the association between the femoral neck BMD and depression ($n = 8$). However, the number of studies that would bring p-value to a number greater than alpha is $n = 130$.

Table 1

Synopsis of 20 eligible articles for meta-analysis of bone mineral density in subjects with depression

Authors, Year [Reference]			Main Findings
Study	Gender/Sample Size	Characterization of Depression	
Design	Age (years)	Skeletal	
Setting	Ethnicity/Race	Sites/Fractures	
Location	Menopausal Status		
Altindag et al., 2007 [5] Cross-sectional Outpatient Clinic for Physical Medicine and Rehabilitation Turkey	Women with MDD (n = 36) Control women matched by age, BMI, age at menarche, number of pregnancies (n = 41) Age: 4 th decade Caucasian All premenopausal	DSM-IV Hamilton depression scale Duration of depression assessed Not on antidepressants at time of evaluation Lumbar spine and femoral neck BMD by DXA	Women with MDD had ↓ BMD at the spine and femoral neck None had osteoporosis ↑ 8 AM Cortisol ↑ C-telopeptide ↓ Osteocalcin No differences in alkaline phosphatase and PTH
Diem et al., 2007 [6] Prospective cohort study Multicentric US Notes: Public funding (NIH) Conflict of interest disclosed	Women (n = 2 722) Age: 7 th decade Black women excluded All postmenopausal	CDS 118 TCA users, 198 SSRI users, 2 406 with no antidepressants Total femur BMD by DXA (Hologic), two evaluations 4.9 ± 0.6 years apart	TCA users: no accelerated bone loss SSRIs users: ↑ Rate of bone loss at the total femur (0.77 %/year in users vs. 0.49 %/year in nonusers)
Eskandari et al., 2007 [7] Cross-sectional evaluation of a prospective cohort (POWER Study) US Notes: Public funding (NIH) No conflict of interest to disclose	Women with current or past MDD (n = 89) Control women matched by age, BMI, race (n = 44) Age: 3 rd decade Women with MDD: 82 whites, 7 blacks Controls: 39 whites, 5 blacks All premenopausal	DSM-IV; Hamilton depression scale Duration of depression assessed 73 women with MDD on antidepressants Spine, total femur, femoral neck, and radius BMD by DXA (Hologic)	Women with MDD: ↓ BMD at the spine and femoral neck ↑ Prevalence of low BMD at the femoral neck and total femur 2/89 women with MDD had osteoporosis ↑ Proinflammatory and ↓ anti-inflammatory cytokines ↑ Bone-specific alkaline phosphatase ↓ 25-OH Vitamin D = osteocalcin
Jacka et al., 2005 [8] Prospective study of an age-stratified, community sample Geelong Osteoporosis Study Australia Note: “Public funding”	Women (n = 78) Age: 50–53 (on average) Ethnicity/race undefined All perimenopausal	Self-reported questionnaire for depression based on the DSM-IV criteria AP spine, total femur, femoral neck, Ward triangle, and trochanter BMD by Lunar Note: No quantitative data reported for femoral neck	In women with depression age-, weight-, and HRT-adjusted BMD was 7.8 % lower at the total femur and tended to be ~5 % lower at the AP spine
Konstantynowicz et al., 2005 [9] Consecutive clinical series of girls with anorexia nervosa (AN) Cross-sectional Poland	Caucasian “adolescent” girls (n = 45) Age: 13 to 23 Caucasian All premenopausal	Hamilton depression scale (cutoff of 13 or higher) and Montgomery–Ashberg depression rating scale (cutoff of 16 or higher) Lumbar spine by DXA (Lunar)	Girls with AN and depression (n = 14): Had lower BMD than girls with AN only (n = 31) (Z score: −2.6 vs. −1.71) BMD was inversely related with depression scores Two girls with AN reported fractures (wrist and ankle)
Özsoy et al., 2005 [10] Cross-sectional Inpatient series in a psychiatric setting Turkey	Patients with depression (n = 21 men; 21 women) Healthy controls (n = 11 men; 12 women) Age: 18–55 (average age: patients 37, controls 34) Turkish All women premenopausal	DSM-IV Severity of symptoms by Montgomery–Asberg depression rating scale Disease duration and number of episodes recorded Spine and total femur BMD by DXA (Hologic 4 500)	No differences in BMD between patients and controls

Authors, Year [Reference]			Main Findings
Study	Gender/Sample Size	Characterization of Depression	
Design	Age (years)	Skeletal	
Setting	Ethnicity/Race	Sites/Fractures	
Location	Menopausal Status		
Wong et al., 2005 [11] Cross-sectional Cohort of community living men China Note: "Public funding"	Stratified sample of men with depression (n = 169) Healthy control men (n = 1 830) Age: 65 or older (average age 72) Chinese	Chinese version of the Geriatric Depression Scale (cutoff of 8 or more) Lumbar spine and total hip by BMD (Hologic 4 500), fractures assessed by medical history	8.5 % of men met criteria for clinical depression These men were more likely to be single, divorced or separated, and had fewer years of formal education than controls Depression was inversely related with total femur BMD Adjusted femur BMD was 2.1 % lower in depressed than nondepressed men (relative risk 1.4, 95 % CI 1–2.08; p = 0.05) Adjusted AP spine BMD was not different between groups Fracture rates were not different between groups
Yazici et al., 2005 [12] Cross-sectional Consecutive patient series in a psychiatric setting Turkey	Women with MDD (n = 35) Control women matched by age, BMI, age at menarche, number of pregnancies (n = 30) Age: 4 th decade Turkish All premenopausal	DSM IV Hamilton depression scale Spine and femoral neck by BMD (Norland XR)	No differences in BMD, 8 AM Cortisol, osteocalcin between groups
Mussolino et al., 2004 [13] Cross-sectional A national probability sample of the civilian non institutionalized US population from 1988 to 1994 (NHANES III Study) US Note: "Public funding"	Probability sample of men (n = 2 528) and women (n = 2 643) Age: 20–39 253 Non-Hispanic white women with MDD 105 Non-Hispanic white men with MDD 30 Non-Hispanic black women with MDD 14 Non-Hispanic black men with MDD 14 Mexican-American women with MDD 8 Mexican-American men with MDD 1844 Non-Hispanic white women w/o MDD 1899 Non-Hispanic white men w/o MDD 352 Non-Hispanic black women w/o MDD 305 Non-Hispanic black men w/o MDD 150 Mexican-American women w/o MDD 197 Mexican-American men w/o MDD All women premenopausal	Diagnostic Interview Schedule (DIS), a structured interview derived from the DSM-III for MDD and dysthymia Total femur BMD by DXA (Hologic)	No differences in BMD in women Men with MDD had 5.1 % lower BMD than men w/o MDD Risk-adjusted odds ratio for men: MDD 1.65, 95 % CI 1.08–2.52; p = 0.05; dysthymia 1.84, 95 % CI 1.29–2.62; p = 0.01) Threshold effect: men with 5 or more symptoms had 3.0 % lower BMD than men with 4 or less symptoms No effects of race/ethnicity
Petronijevic et al., 2004 [14] Cross-sectional Psychiatric clinic Yugoslavia	Women with depression (n = 23) Healthy control women (n = 22) Age: "premenopausal" All premenopausal	DSM-IV Lumbar spine, total femur BMD by DXA (Lunar DPX-IQ)	Duration/severity of depression had strong negative correlation with BMD

Authors, Year [Reference]			Main Findings
Study	Gender/Sample Size	Characterization of Depression	
Design	Age (years)	Skeletal	
Setting	Ethnicity/Race	Sites/Fractures	
Location	Menopausal Status		
Whooley et al., 2004 [15] Prospective cohort study for risk factors of osteoporosis in older men US Note: “Public funding”	White men evaluated at baseline (n = 523) A random subset (n = 100) evaluated 3.6 years later Age: 6 th decade	GDS Lumbar spine, total femur BMD by DXA (Hologic)	No association between depressive symptoms and adjusted BMD No differences in adjusted BMD in subjects with 6 or more depressive symptoms vs. subjects with 5 or fewer symptoms 3.1 % of men had depression (GDS >6) at baseline; 4 % at follow-up
Thomas et al., 2003 [16] Cross-sectional Psychogeriatric setting France	Patients (n = 64; 44 women, 20 men) Age:80.6±7.1 All women postmenopausal	Cornell’s scale Femoral neck BMD by DXA (Hologic)	↓ BMD in subjects with depression
Yazici et al., 2003 [17] Cross-sectional Consecutive series of psychiatric patients Turkey Note: Funded in part by a pharmaceutical company	Untreated women with MDD (n = 25) Healthy control women with similar BMI, age, calcium intake, physical activity, social class (n = 15) Age: 3rd decade All premenopausal	DSM-IV Lumbar spine, total femur, femoral neck, Ward triangle, trochanter BMD by DXA (Hologic)	An amount of 12 % and 10 % lower BMD at the AP spine and femur, respectively, in women with MDD vs. controls No differences in 8 AM Cortisol, and bone biochemical markers, including osteocalcin
Kavuncu et al., 2002 [18] Cross-sectional Patient series Turkey	Women with MDD(n = 42), 11 women on SSRIs Healthy control women with similar BMI and age (n = 42) Age: 3rd decade Turkish All premenopausal	DSM-IV Hamilton depression scale Lumbar spine, total femur, femoral neck, Ward triangle and trochanter BMD by DXA (Hologic)	No differences in BMD between women with MDD and controls Higher BMD in women with MDD on SSRIs ↑ Urinary deoxypyridinoline in women with MDD No differences in osteocalcin, alkaline phosphatase, and 8 AM ACTH and Cortisol between groups
Robbins et al., 2001 [19] Prospective population-based cohort Cardiovascular Health Study US Note: Funded by NHLBI and Georgetown University, Washington DC	Men and women (n = 1 552) 716 Caucasian women 536 Caucasian men 187 African-American women 113 African-American men Age: 65–100 All women postmenopausal	Modified 10-item version of the Center for Epidemiological Studies Depression Scale (CES-D: cutoff for depression: 10) Total femur BMD by DXA (Hologic)	16 % of participants were clinically depressed; 9 % had BMD in the osteoporotic range Depression was negatively associated with total femur BMD in the entire cohort, and among Caucasians and African-American After adjustments, depression accounted for 2 % of the total femur BMD variability One point increase in depression scores CES-D was equivalent to an increase in age of approximately 2 years
Reginster et al., 1999 [20] Cross-sectional Consecutive series of patients attending an osteoporosis clinic Belgium	Women never treated for osteoporosis (n = 121) Age: 48–77 Caucasian? All postmenopausal	General Health Questionnaire, a 28-item self-administer instrument covering depression, anxiety, somatic factors and physical dysfunction (GHQ-28) Spine, total femur, femoral neck BMD by DXA (Hologic)	No relationship between depression (GHQ-28 scores) and BMD

Authors, Year [Reference]			Main Findings
Study	Gender/Sample Size	Characterization of Depression	
Design	Age (years)	Skeletal	
Setting	Ethnicity/Race	Sites/Fractures	
Location	Menopausal Status		
Whooley et al., 1999 [21] Prospective population-based cohort study 4 centers (Study of Osteoporotic Fractures, SOF) US Note: Public funding (US Veterans Administration and Public Health Service)	All women (n = 7 414) Age: 7 th decade (at least 65 years old) White All postmenopausal	GDS (depression defined as a score of >6) Spine total femur, Ward triangle, trochanter BMD by DXA (Hologic) Self-reported incident falls (vertebral fractures by histomorphometry and nonvertebral fractures by self-report)	An amount of 6.3 % prevalence of depression No differences in adjusted BMD between women with and without depression in the whole cohort In the highest tertile of BMI (>27.6), spine BMD was 4.6 % lower and femur BMD was 2.6 % lower in women with depression Women with depression were more likely to fall (age-adjusted O.R. 1.6; 95 % CI 1.3–1.9; p = 0.001) More vertebral and non-vertebral fractures in women with depression (age-adjusted O.R. for vertebral fractures: 2.3, 95 % CI 1.6–3.2; p = 0.001; age-adjusted O.R. for nonvertebral fractures: 1.4, 95 % CI 1.2–1.7; p = 0.001)
Amsterdam et al., 1998 [22] Cross-sectional Patient series US Note: Funded by University of Pennsylvania Medical Center, Philadelphia	Patients with depression (n = 6; 4 women, 2 men) Healthy controls (n = 5; 3 women, 2 men) Age: 4 th decade Ethnicity/race: unspecified Women with depression (n = 4): 3 premenopausal, 1 postmenopausal Control women (n = 3): all premenopausal	DSM III-R Hamilton depression scale Spine BMD by DXA (Lunar)	No differences in BMD or urinary free Cortisol between groups
Michelson et al., 1996 [23] Cross-sectional Patient series US Note: Public funding (NIH)	Women with past or current MDD (n = 24) Control women matched by age, BMI, menopausal status, race (n = 24) Women with MDD: 22 whites, 2 blacks Control women: 19 whites, 2 blacks, 3 Asians Age: 41 (on average) 22 premenopausal, 2 postmenopausal in both groups	DSM-III R Hamilton depression scale Spine, femoral neck, Ward triangle, trochanter, radius BMD by DXA (Hologic)	Lower BMD in women with MDD: –6.5 % at the spine; –13.6 % at the femoral neck and trochanter ↑ UFC ↓ Serum osteocalcin ↓ Urinary deoxypyridinoline
Schweiger et al., 1994 [24] Cross-sectional Patient series Germany Note: Funded by Max Planck Institute	Patients with MDD (n = 80; 53 women; 27 men) Age: 40 or older Caucasian? Healthy comparison subjects (n = 57; 27 women; 30 men) All women postmenopausal	DSM-III R Lumbar spine by CT	After adjustment for age, spine BMD 15 % lower in patients with MDD

AN: anorexia nervosa; BMC: bone mineral content; BMD: bone mineral density; BPD: borderline personality disorder; CT: computer tomography; DSM: disease state manual; GDS: geriatric depression scale; GHQ: general health questionnaire; HRT: hormone replacement therapy; MDD: major depressive disorder; OR: odds ratio; PTH: parathyroid hormone; TCA: tricyclic antidepressants; SSRI: serotonin selective reuptake inhibitors; UFC: urinary free Cortisol

Table 2

Synopsis of 13 articles on bone mineral density in subjects with depression not included in meta-analysis

Author, Year [Reference]	Sample Size, Gender	Characterization of Depression	Main Findings
Study Design	Age (years)	Skeletal Sites/Fractures	
Setting	Menopausal Status		
Location			
Funding			
Conflict of Interest			
Dorn et al., 2008 [25] Observational prospective study (baseline analysis) Community/urban teen health center US Notes: Public funding (NIH, Public Health Service, National Center for Research Resources) No conflict of interest to disclose	Girls (n = 207) Age: enrolled at 11, 13, 15, and 17 125 whites, 65 African-Americans, and 11 others All premenopausal	Children's Depressive Inventory State-Trait Anxiety Inventory Questionnaire on tobacco use Whole body, lumbar, femoral BMD, and BMC by DXA	After adjustment for covariates, higher depressive symptoms were associated with lower (1.4–6.5 %) total BMC Among White participants, higher state anxiety was associated with lower total BMC No effects of smoking on bone health
Petronijevic et al., 2008 [26] Cross-Sectional Psychiatric clinic Serbia	Women with unipolar depression (n = 73) Control women matched by age and osteoporosis risk factors (n = 47) Age: 4 th decade of age Caucasian All premenopausal	DSM-IV Hamilton depression scale Duration of depression assessed Lumbar spine, femoral BMD by DXA (Lunar DPX-IQ)	Approximately 45 % of women with depression had osteoporosis >↓ BMD at the spine and femoral neck Duration of depression was inversely related to BMD Use of antidepressant was not related to BMD ↑ Markers of bone resorption (5b-tartrate resistant acid phosphatase, urine NTX) directly related to severity of depression No differences in Cortisol, PTH, and estradiol
Diem et al., 2007 [27] Prospective cohort study 4 centers (Osteoporotic Fractures Study, SOF) US Notes: Public funding (NIH) Conflict of interest disclosed	Women with depressive symptoms (GDS score >6)(n = 200) Control women (GDS <6) (n = 3 977) Age: 7 th decade Black women excluded All postmenopausal	GDS, a 15-item self-report depressive symptoms checklist Antidepressant use: 12.5 % in depression, 4 %: in controls Total femur, femoral neck, trochanter BMD by DXA (Hologic), 4.9 ± 0.6 years after first evaluation	Women with depression had: ↑ Rate of bone loss at the total femur, and femoral neck (0.96 %/year vs. 0.69 %; depressed vs. controls); Results unchanged when antidepressant users excluded
Niti et al., 2007 [28] Cross-sectional study of a prospective cohort Community sample Singapore Notes: Public funding (NIH) No conflict of interest to disclose	Community sample (n = 2 611; 963 men, 1648 women) Age: 6 th decade of age Ethnicity/race: unspecified All women postmenopausal	GDS Osteoporosis assessed by medical history	↑ Risk of having osteoporosis if depressed: (O.R. 2.32; 95 % CI 1.13–4.76)
Silverman et al., 2007 [29] Cross-sectional (randomized, controlled, prospective clinical trial of raloxifene) Multicentric (180 centers) (MORE Study) International (25 countries)	Women with osteoporosis (T score <2.5) (n = 3 798) Age: 6 th decade Ethnicity/race: unspecified All postmenopausal	GDS Prevalent vertebral fractures, as assessed by semiquantitative vertebral radiograph	Prevalence of probable depression was greater in women with a vertebral fracture vs. no fracture (6.6 % vs. 4.1 %) Prevalence of probable depression was 3-fold higher in women with at least 3 probable vertebral fractures compared to women without prevalent vertebral fractures

Author, Year [Reference]	Sample Size, Gender	Characterization of Depression	Main Findings
Study Design	Age (years)	Skeletal Sites/Fractures	
Setting	Menopausal Status		
Location			
Funding			
Conflict of Interest			
Tolea et al., 2007 [30] Prospective cohort Multi-state community-dwelling sample US Note: Public funding (NIH)	Mexican-American women with depressive symptoms (n = 1 350) Age: 7 th decade All postmenopausal	Center for Epidemiological Studies Depression Scale Self-reported new diagnoses of osteoporosis or any fracture	High depressive symptomatology predictive of self-reported osteoporosis (O.R. 1.42; 95 % CI 1.05–1.92) Self-reported fractures (OR. 1.43; 95 % CI 1.03–1.99)
Kahl et al., 2006 [31] Cross-sectional Psychiatric outpatient clinic Germany Note: Public funding (University)	Women with BPD and MDD (n = 23), MDD only (n = 24), BPD only (n = 16) Healthy control women (n = 20) Age: 2nd–4 th decade Caucasian All premenopausal	DSM-IV Spine, femoral neck, radius BMD by DXA (Lunar) No information on fractures	AP spine ~9 % lower in subjects with MDD/BPD vs. BPD only or MDD only older than 43 ↑ Osteocalcin (~30 %) ↑ Cross-laps (~40 %) ↑ TNF-α and IL-6 (~25 % and ~100 % in MDD/BPD vs. controls ↑ Osteoprotegerin (~25 % in subjects with MDD <30 years vs. all other groups) No differences in estradiol, 1,250H–Vitamin D, PTH, leptin, and AM Cortisol
Korpelainen et al., 2006 [32] Cross-sectional Birth cohort (secondary analysis) Finland Note: “Public funding”	Out of the original birth cohort (n = 1 222), only women in the lowest BMI tertile (below 25.1, mean BMI 23; n = 407) were included Ethnicity/race: unspecified Age: 7 th decade All postmenopausal	GDS Radius, calcaneum BMD by DXA (Hologic) Self-reported fractures	Depression (GDS score >8) increases risk of falling as much as impaired vision (O.R. 2.3; CI 1.2–4.4) No association between BMD and depression
Bianchi et al., 2005 [33] Cross-sectional consecutive clinical series Outpatient clinic Italy	Women with osteoporosis (n = 100: 38 with vertebral fractures); control women with hypothyroidism (n = 35) Age: 5 th –8 th decade Caucasian All postmenopausal	Zung depression scale Quality of life (Qualeffo-41) Lumbar spine, proximal femur BMD (DXA by Hologic) Vertebral fractures confirmed by x-rays	A sum of 40 % of women with osteoporosis had depressive symptoms vs. 23 % of women with hypothyroidism
Cankurtaran et al., 2005 [34] Cross-sectional consecutive series Outpatient geriatric clinic Turkey	Men and women (n = 1 255) Age: 5 th –9 th decade Turkish All women postmenopausal	GDS Clinical diagnosis of osteoporosis	Depression more prevalent in subjects with osteoporosis (25 % vs. 17 % p = 0.001; O.R. 1.54; 95 % CI 1.16–2.05)
Kahl et al., 2005 [35] Cross-sectional consecutive series Outpatient psychiatric clinic Germany Note: Funded by University of Lubeck	Women with BPD (n = 38; 22 with MDD, 16 w/o MDD) Healthy women (n = 20) Age: 2nd–3rd decade Caucasian All premenopausal	DSM-IV Lumbar spine, total femur, radius BMD by DXA (Lunar)	↓ BMD in women with BPD and current MDD (n = 10) vs. women with BPD only (n = 22) or healthy women ↑ Cortisol, TNF-α, IL-6, and cross-laps in women with BPD and current MDD (n = 10) vs. healthy women TNF-α inversely related to AP spine Z scores
Mussolino 2005 [36] Prospective cohort study National probability sample (NHANES I Study) US	White and black men and women (n = 6 195) Women = 3350 Men = 2845 White = 5445	General Well-Being Schedule, a 4-item questionnaire rating the severity of depression over the past month Femur fractures assessed by hospital records	Depression predictive of femur fracture (HR 1.9, 95 %; CI 1.1.3–3.21; p = 0.01);

Author, Year [Reference]	Sample Size, Gender	Characterization of Depression	Main Findings
Study Design	Age (years)	Skeletal Sites/Fractures	
Setting	Menopausal Status		
Location			
Funding			
Conflict of Interest			
Note: Public funding (Center for Disease Control, CDC)	Black = 750 Age: 25–74 Women pre- and postmenopausal (proportions not specified)	Mean duration of follow-up: 22 years	After adjustments, the HR remained high (HR 1.7; 95 % CI 0.99–2.91; $p = 0.0550$) Threshold effect: subjects with high depressive symptoms had greater (almost double) risk of fractures than those with intermediate or low symptoms Individuals reporting higher depressive scores more likely to be female, black, and having a higher BMI
Schweiger et al., 2000 [37] Cross-sectional (follow-up evaluation) Patient series Germany	Patients with depression ($n = 18$; 8 women, 10 men) Comparison subjects ($n = 21$; 7 women, 14 men) Age: 40 and older All women postmenopausal Note: Subjects were included if >40 year old and original evaluation was 24 months earlier	DSM-III R Bone density of L1 and L3 by single energy quantitative CT	Annualized bone loss accelerated in subjects with depression compared to comparison subjects: $6.9 \pm 5.5 \text{ mg/cm}^3$ vs. 3.9 ± 4.2 in men; $3.8 \pm 4.3 \text{ mg/cm}^3$ vs. 0.9 ± 8.2 in women

AN: anorexia nervosa; BMC: bone mineral content; BMD: bone mineral density; BPD: borderline personality disorder; CT: computer tomography; DSM: disease state manual; GDS: geriatric depression scale; GHQ: general health questionnaire; HRT: hormone replacement therapy; MDD: major depressive disorder; OR: odds ratio; PTH: parathyroid hormone; TCA: tricyclic antidepressants; SSRI: serotonin selective reuptake inhibitors; UFC: urinary free Cortisol

Table 3

Qualitative summary of reports on depression and osteoporosis

Study Characteristic	Meta-analysis (n = 20) Depression associated with lower BMD (positive studies)	Depression not associated with lower BMD (negative studies)	Research synthesis only (n = 13) Depression associated with lower BMD (positive studies)	Depression not associated with lower BMD (negative studies)
Subgroup Analysis				
Overall	13 [5–9, 11, 13, 14, 16, 17, 19, 23, 24]	7 [10, 12, 15, 18, 20–22]	12 [25–31, 33, 34–37]	1 [32]
Age				
Ages up to 55	7 [5, 7, 9, 13, 14, 17, 23]	4 [10, 12, 18, 22]	5 [25, 26, 31, 35, 36]	0
Ages >55	6 [6, 8, 11, 16, 19, 24]	3 [15, 20, 21]	7 [27–30, 33, 34, 37]	1 [32]
Sample Size				
<500	8 [5, 7–9, 14, 17, 23, 24]	5 [10, 12, 18, 20, 22]	6 [25, 26, 31, 33, 35, 37]	0
>500	5 [10, 12, 18, 20, 22]	2 [15, 21]	6 [27–30, 34, 36]	1 [32]
Menopausal status				
Premenopausal	8 [5, 7, 9, 12–14, 17, 23]	2 [10, 18]	4 [25, 26, 31, 35]	0
Postmenopausal	4 [6, 16, 19, 24]	2 [20, 21]	6 [27–30, 33, 37]	1 [32]
Pre- and postmenopausal	1 [8]	1 [22]	1 [36]	0
Geographic location				
United States	5 [6, 7, 13, 19]	3 [15, 21, 23]	4 [25, 27, 30, 36]	0
Europe	4 [9, 14, 16, 24]	1 [20]	5 [26, 31, 33, 37]	1 [32]
Rest of the world	4 [5, 8, 11, 17]	3 [10, 12, 18]	3 [28, 29, 34]	0

Numbers in square brackets denote reference numbers