A meta-analysis of prevalence estimates and moderators of low bone mass in people with schizophrenia

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Abstract

Objective

To assess the prevalence and moderators of low bone mass, osteopenia and osteoporosis in schizophrenia patients.

Method

Major electronic databases were searched from inception till 12/2013 for studies reporting the prevalence of low bone mass (osteopenia + osteoporosis = primary outcome), osteopenia or osteoporosis in schizophrenia patients. Two independent authors completed methodological appraisal and extracted data. A random effects meta-analysis was utilised.

Results

Nineteen studies were included (n=3,038 with schizophrenia; 59.2% male; age 24.5-58.9 years). The overall prevalence of low bone mass was 51.7% (95% CI=43.1-60.3%); 40.0% (CI=34.7-45.4%) had osteopenia and 13.2% (CI=7.8-21.6%) had osteoporosis. Compared with controls, schizophrenia patients had significantly increased risk of low bone mass (OR=1.9, CI=1.30-2.77, p<0.001, n=1,872) and osteoporosis (OR=2.86, CI=1.27-6.42, p=0.01, n=1,824), but not osteopenia (OR=1.33, CI=0.934-1.90, p=0.1, n=1,862). In an exploratory regression analysis, older age (p=0.004) moderated low bone mass, whilst older age (p<0.0001) and male sex (p<0.0001) moderated osteoporosis. The subgroup analyses demonstrated high heterogeneity, but low bone mass was less prevalent in North America (35.5%, CI=26.6-45.2%) than Europe (53.6%, CI=38.0-68.5%) and Asia (58.4%, CI=48.4-67.7%), and in mixed in-/outpatients (32.9%, CI=49.6-70.1%) versus inpatients (60.3%, CI=49.6-70.1%).

Conclusion

Reduced bone mass (especially osteoporosis) is significantly more common in people with schizophrenia than controls.

Summations

- Low bone mass affects more than half of patients with schizophrenia and is approximately twice as common compared to age- and sex-matched controls.
- Osteoporosis is over two and a half times more common in patients than in controls.
- Multidisciplinary teams should routinely screen and implement appropriate interventions targeting bone health.

Considerations

- There was a paucity and inconsistency in the reporting of factors that may influence the prevalence of low bone mass across studies.
- All of the studies included were cross-sectional; therefore directionality of the association between the variables investigated and the observed low bone mass cannot be deduced with certainty.
- We could not clearly elucidate the influence of antipsychotics since there were inadequate data on specific medications.

Key words: Bone Mineral Density; Bone Mass, Osteoporosis, Osteopenia, Schizophrenia, Physical health, Antipsychotics, Meta-analysis; Hyperprolactinemia, Screening

MESH: Osteoporosis/epidemiology*, Bone Density, Risk Factors, Antipsychotic Agents, schizophrenia, physical activity

Introduction

Osteoporosis is a progressive systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue resulting in a profound increased fracture risk (1, 2). Osteoporosis is a global public health concern, affecting more than 200 million people worldwide (3) and the associated fractures are related with increased morbidity and mortality (2, 4). Awareness of the elevated risk of osteoporosis, osteopenia, which is a precursor to osteoporosis but not a disease category in its own right, and low bone mass in schizophrenia is increasing (5, 6). However, research investigating bone health lags behind progress in other medical areas, such as obesity and metabolic syndrome (7, 8). Schizophrenia patients are thought to be at risk of low bone mass (including osteoporosis and osteopenia) due to antipsychotic-induced hyperprolactinemia (6, 7, 9, 10) and a plethora of lifestyle influences, including physical inactivity (5, 8). In non-mental health settings, common risk factors increasing a person's propensity for osteoporosis include smoking (11), physical inactivity, polydipsia, alcoholism, alcohol misuse, hypogonadism, a family or personal history of fractures and vitamin D deficiency (3, 4). Smoking (12), physical inactivity (13, 14) and vitamin D deficiency (15) are all increased in schizophrenia patients and when coupled with the increased threat of hyperprolactinaemia (16), the risk of low bone mass is in this population is considerable. These factors may explain why two recent, large population-cohort studies (17, 18) found that people with schizophrenia are at significantly increased risk of hip fractures compared to the general population. This is concerning since the impact of hip fractures in people with serious mental illness, including schizophrenia, is profound and may lead to a worsening mental state (8), higher post-operative infection rates, worse ambulatory rates after one year, and a risk of contralateral fractures (9).

Recently, several reviews have investigated the influence of antipsychotics on osteoporosis, (6, 19, 20) whilst other narrative reviews (5, 7, 21) have considered the prevalence of osteoporosis in

schizophrenia. However, to our knowledge, no meta-analysis has assessed the prevalence and moderators of low bone mass, osteopenia and osteoporosis in schizophrenia.

Aims of the study

In order to determine the degree of low bone mass in people with schizophrenia, we conducted a systematic review and meta-analysis with three aims: 1) to investigate the prevalence of low bone mass (osteoporosis and osteopenia combined), b) osteopenia and c) osteoporosis in people with schizophrenia. 2) To compare the prevalence of low bone mass, osteoporosis and osteopenia between people with schizophrenia and age- and sex-matched control subjects. 3) To assess if sex, age, smoking status, prolactin-raising antipsychotic use, illness duration, geographical region, setting (in- or outpatient) and the assessment method used to quantify low bone mass in people with schizophrenia moderated the prevalence of low bone mass, osteoporosis and osteopenia.

Method

Inclusion and exclusion criteria

This systematic review was executed according to Meta-analysis of Observational Studies in Epidemiology guidelines (MOOSE) (22) and reported according to the PRISMA statement (23) following an a-priori but unpublished protocol. We included observational studies published in any language that measured skeletal status or bone mineral density (BMD) and reported prevalence of osteoporosis (T-scores of <2.5 or Z-score <2) or osteopenia (T-scores of -1 to -2.5 or Z-score <1) according to the World Health Organization criteria (24) in patients with a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual (DSM IV;(25)) or International Classification of Disease (ICD 10;(26)) criteria. We also included mixed samples of patients with schizophrenia or schizoaffective disorder, but only when >80% had schizophrenia and the corresponding author could not provide separate data for schizophrenia patients only. The primary outcome was the prevalence of low bone mass, defined as the combined prevalence of osteoporosis and osteopenia in each sample measured with T-score (standard deviation for peak bone mass for sex, 24). If this was not available, we used the Z-score (standard deviations from subjects of similar age, gender and ethnicity). We included studies that reported the prevalence of low bone mass with T- or Z-scores measured by either dual-energy X-ray absorptiometry (DXA) or quantitative ultrasound (QUS). QUS is highly correlated with BMD measured by DXA and is able to predict future fractures (27). In each analysis, we pooled the prevalence estimates determined by DXA and QUS together, but conducted sensitivity analyses to determine the influence of the method of measurement upon the results. In order to reduce heterogeneity, wherever possible we used the T score measured with DXA at the lumbar spine since measurements at this site are recommended by international guidelines (4). When we identified a study that measured bone mass in patients with schizophrenia, but the prevalence was not reported, we contacted the authors up to three times over one month requesting the missing information.

Studies were excluded that did not: (a) provide prevalence of osteopenia or osteoporosis according to a T- or Z-score in line with the WHO-criteria; (b) confirm a diagnosis of schizophrenia with DSM-IV or ICD-10 criteria; (c) had insufficient data and/or the authors did not provide sufficient information in response to requests for prevalence data. In the case of multiple publications from the same study, only the most recent paper or article with the largest sample with complete data was included.

Literature search and critical appraisal

Two authors (BS, DV) independently searched PubMed, Academic Search Premier, Psychology and Behavioural Sciences Collection, PsycINFO, EMBASE and CINAHL from inception until 5th December 2013. We used the following search terms: (osteoporosis or osteopenia or osteo* or bone mineral density or DXA or DEXA or bone) AND (schizophrenia or schizo* or psychosis). Both authors independently screened titles and abstracts of all articles, and a list of articles was selected by consensus for full text review. A third reviewer was available for mediation. Subsequently, both authors independently reviewed the reference lists of recent systematic reviews on this topic (5-7, 9, 16, 20, 21).

All included articles underwent methodological quality assessment by two appraisers with the Newcastle Ottawa Scale (NOS). The NOS is a tool used to assess the quality of observational studies (28) and its reliability and validity have been established. Scores of 6 or greater are considered good methodological quality (28).

Data extraction

Two independent authors (BS, DV) extracted information from each study including the region the study was conducted, setting (inpatients, outpatient or mixed, i.e. in- and outpatients in the same study), socio-demographic information of patients and controls, details of known risk

factors for osteoporosis where available (body mass index (BMI), % smokers, type of antipsychotic medication, % patients taking prolactin-raising antipsychotics (first-generation antipsychotics and amisulpride, paliperidone and risperidone) (16), duration of antipsychotic treatment, duration of schizophrenia, percentage of patients with hyperprolactinaemia, serum osteocalcin levels, serum vitamin D levels, family/personal history of fractures, and menopausal status for females).

Data synthesis and analysis

Due to the anticipated heterogeneity, (22) all analyses were conducted with a random effects model using Comprehensive Meta-Analysis Version 2.0. For aim 1, we calculated an aggregate event rate (prevalence) for all studies reporting prevalence of low bone mass, osteopenia, and osteoporosis in patients with schizophrenia. We calculated the odds ratios (OR) to compare the prevalence of low bone mass, osteoporosis and osteopenia between individuals with schizophrenia and general population control subjects (Aim 2).

For aim 3, subgroup analyses were carried out on continuous data examining whether the observed variance was significantly explained by continuous variables, such as mean age of the study sample, mean BMI, percentage of male participants, percentage of smokers, percentage with hyperprolactinemia, percentage of postmenopausal women, and percentage of patients taking prolactin-raising antipsychotics. The results of the exploratory moderator analysis were subjected to a Bonferroni correction. The global analyses were also subjected to categorical variable data analyses to examine the effect of these variables on the existing heterogeneity. We conducted numerous subgroup analyses and calculated the prevalence of low bone mass, osteoporosis and osteopenia according to geographical area (North America, Asia, Europe and South America), prolactin-raising antipsychotic medication (yes, mixed, unclear), method to measure bone mass (DXA versus QUS), definition of low bone mass (T-scores and Z-scores) treatment setting (outpatients versus inpatients and mixed), and methodological quality (high NOS scores ($\geq$6) versus

medium and low scores (≤5). The MOOSE (22) guidelines recommend that authors conduct subgroup analyses to explore possible sources of anticipated heterogeneity.

To examine the homogeneity of the effect size distribution, the Q-statistic (29) and I^2(30) were used. When the Q-statistic is rejected, the effect size distribution is not homogeneous, implying that the variability in the aggregate prevalence of low bone mass, osteoporosis and osteopenia between studies is larger than can be expected based on sampling error alone. To examine for publication bias two methods were used concurrently; a) the Begg and Mazumdar's rank correlation test (31); and b) the parametric Egger test(32). All confidence intervals are presented at 95%.

Results

Search results, studies and participants

The initial electronic search yielded 689 valid hits and 19 studies were included in the meta-analysis (33-51). At the full text viewing stage, we contacted the authors of 25 publications and of these 8 studies were subsequently included (5 authors provided additional data, see acknowledgments, and 3 authors did not respond, but contained sufficient data within the paper to enable inclusion), and 17 were excluded due to insufficient data. Full details of the search results and reasons for exclusion are summarized in figure 1.

Figure 1 here

In total, the dataset included 3,038 schizophrenia patients. The sample size in each study ranged from 10 (42) to 965 (48). The mean age of participants was 42.7 years (range: 24.5 (44) to 59.1 (37) years) and the mean percentage of males was 59.2%. Eight studies were conducted in Asia (36, 37, 39-41, 47, 48, 50), 7 in Europe (33, 34, 44-46, 49, 51) and 4 in North America (35, 38, 42, 43). Eight studies (36, 37, 39-41, 48-50) (n=1,883) were conducted in inpatient settings, 6 included outpatients (33, 34, 42, 43, 45, 46) (n=525), 4 studies included participants from mixed settings (35, 38, 44, 51) (n=545), and the setting was unclear in one study (47) (n=85). All studies undertook a cross-sectional measurement of bone mass. Details on the included studies and the participants are presented in table 1. Five studies were considered of high methodological quality scoring 6 and above on the NOS (33, 36, 37, 44, 51) and the rest were categorized as being of medium/low quality. (see table 1).

Table 1 here

There was considerable inconsistency in the reporting of the investigated risk factors for osteoporosis. For instance, six studies provided illness duration with an average of 18.4 years (range: 9.75 (35) to 34.6years (40)), 7 studies provided details about the duration of antipsychotic treatment with a mean of 14.2 years (range: 0.2 (44) to 29.6years (40)), ten studies provided details of the

percentage of participants taking prolactin-raising antipsychotics (range: 18.6% (35) to 100% (43, 45)), and 8 studies provided details of the percentage of patients with hyperprolactinaemia (range: 28% (35) to 84.6% (40)). Data were available for vitamin D (33) and osteocalcin (35) levels in only one study each. The reporting of lifestyle-related factors also varied; 6 studies reported on the prevalence of smoking (range: 29% (36) to 58% (44)), 9 studies reported on BMI; range: 21 (44) to 30.3 (45)), and 5 studies (40, 41, 45, 46, 49) reported on physical activity through a range of methods and subsequent outputs.

Of the 19 studies, 14 utilized a DXA scanner (33-37, 40-42, 44-47, 49, 51) (n=828 with schizophrenia) and 5 studies used QUS (38, 39, 43, 48, 50) (n=2,210 with schizophrenia).

Only eight studies had a control group, but one (48) was not matched for age and was excluded from pooled analysis comparing patients with controls (aim 2). In total, 7 studies (33, 36, 37, 42, 44, 50, 51) involving 746 participants with schizophrenia (mean age range: 24.5 (44) to 58.2 (37) years; percentage of males: 0-100%) and 1,126 age- and sex-matched controls (mean age range: 23.7 (44) to 59.0 (37) years; percentage of males: 0-100%) were included in the comparative meta-analysis (aim 2). Details of the prevalence of low bone mass, osteoporosis and osteopenia from each study are summarized in table 1.

Pooled prevalence of low bone mass

The overall pooled prevalence of low bone mass calculated from 18 studies (33-47, 49-51) (n=2,905) was 51.7% (CI=43.05-60.3%; Q=274 (17), $p<0.001$, $I^2=93.8\%$). The Begg-Mazumdar: Kendall's tau (-.04, p=0.8) and Egger's bias tests (-.19, p=0.9) did not demonstrate any evidence of publication bias.

Moderating variables of low bone mass prevalence

Lower bone mass prevalence was significantly associated with older age (N=9; n=370; p=0.004), higher BMI (N=5; n=189; p=0.018) and a higher percentage of post-menopausal females

(N=8; n=305; p=0.016). Conversely, low bone mass was not explained by differences in the percentage of male participants (N=12; n=1,096; p=0.38), people taking prolactin-raising antipsychotics (N=9; n=826; p=0.44), or people with hyperprolactinemia (N=8; n=400; p=0.46) nor the duration of illness (N=4; n=218; p=0.68). After applying a Bonferroni correction, only age remained a significant moderator.

The prevalence of low bone mass was lower in North America (35.3%, CI=26.6-45.2%, N=4, n=835) compared to Europe (53.6%, CI=38.0-68.5%, N=7, n=256) and Asia (58.4%, CI=48.4-67.7%, N=7, n=1814). Studies conducted in inpatient settings had an increased prevalence of low bone mass (60.3%, CI=49.6-70.1%, N=7, n=1,750) than those in mixed settings (32.9%, CI=21.6-46.7%, N=4, n=545,) and outpatient settings (53.6%, CI=35.6-70.9%, N=6, n=525). A full summary of the categorical analyses reporting the prevalence of low bone mass according to geographical region, study setting, prolactin-raising medication, type of bone scan, and methodological quality is presented in table 2.

Table 2 here

Pooled prevalence of osteoporosis

The overall pooled prevalence of osteoporosis in schizophrenia incorporating 17 studies (33-42, 45-51 (n=2,671) was 13.2% (CI=7.8-21.6%; Q= 299.79 (16), p=<0.0001, I^2=94.6%). Neither the Begg-Mazumdar Kendall's tau (-.117, p=0.5) or the Egger's bias tests (-1.6, p=0.3) demonstrated any evidence of publication bias.

Moderating variables of osteoporosis

Osteoporosis was significantly associated with older age (N=8, n=351, p<0.0001), a higher percentage of males (N=11, n=957, p<0.0001) and post-menopausal females (N=6, n=242, p=0.01). The percentage of the sample with hyperprolactinaemia, the percentage of patients taking prolactin-raising antipsychotics, the percentage of smokers, duration of illness and BMI were not related to

the prevalence of osteoporosis. After applying the Bonferroni correction, only older age and a higher percentage of males remained a significant moderator of osteoporosis in patients with schizophrenia.

The prevalence of osteoporosis was lower in North America 4.75% (CI= 1.50-14.0, N=3, n=487) than Europe (15.0%, CI=5.6-34.4, N=6, n=237) and Asia (16.45%, CI=8.12-30.4, N=8, n=1947). A higher prevalence of osteoporosis was found in studies that measured BMD with DXA (15.1%, CI: 9.3-23.7%, N=13, n=809) compared to QUS (10.3%, CI: 2.34-35.9%, N=4, n=1862). There was a higher prevalence of osteoporosis in inpatients settings compared to outpatient settings. A full summary of the subgroup analysis detailing the prevalence of osteoporosis is presented in table 3.

Table 3 here

Pooled prevalence of osteopenia

The overall pooled prevalence of osteopenia calculated from 17 studies (33-38, 40-42, 44-51) (n=2,556) was 40.0% (CI=34.7-45.4%; Q=79.8 (16), p<0.0001, I^2=79.9%). Both the Begg-Mazumdar: Kendall's tau (-.33, p=0.06) and the Egger's bias tests (-.87, p=0.34) failed to find any statistically significant evidence of publication bias.

Moderating variables of osteopenia

Osteopenia was significantly associated with a higher percentage of males (N=10, n=824 p<0.0001) and smokers (N=6, n=173 p=0.01). BMI, older age, percentage of post-menopausal females, illness duration of illness, the percentage with hyperprolactinaemia did not have a significant effect on the prevalence of osteopenia. Only a higher percentage of males remained significant in the moderator analysis after applying the Bonferroni correction.

Studies including participants who all took prolactin-raising antipsychotics had a higher prevalence of osteopenia (49.9%, CI=43.8-55.9%, N=4, n=354) compared to studies in which only

some patients took prolactin-raising antipsychotics (30.0%, CI= 22.7-38.5%, N=6, n=593). Studies reporting osteopenia measured by DXA reported a higher prevalence (40.9%, CI=35.2-46.8%, N=14, N=828) than those using QUS (37.9%, CI: 26.5-50.7%, N=3, n=1729). A full summary of the prevalence of osteopenia according to the geographical region, study setting, type of bone scan and methodological quality is presented in table 4.

Table 4 here

Prevalence of low bone density, osteopenia and osteoporosis in patients with schizophrenia compared to matched controls

Patients with schizophrenia (n=746) had a significantly increased risk of low bone mass compared to controls (n=1,126, OR=1.9, CI=1.30-2.77, p<0.001). This remained evident when analyzing only studies that used DXA scans (n=679, OR=2.28, CI=1.60-3.23, p<0.0001). The pooled risk of osteoporosis was significantly higher in patients with schizophrenia (n=717) vs. controls (n=1107) (n=5 studies; OR=2.86, CI=1.27-6.42, p=0.01) and this was also the case when only analyzing studies using DXA scores (schizophrenia (n=355) vs. controls (n=275): OR=2.23, CI=1.40-3.56, p=0.0007). The pooled risk of osteopenia was not significantly increased in patients with schizophrenia (n=735) compared to controls (n=1,127) in the pooled analysis involving 6 studies (OR=1.33, CI=0.934-1.90, p=0.1). The same was true in the studies using DXA scans (schizophrenia (n=373) versus controls (n=492): OR=1.65, CI=0.94-2.90, p=0.07).

Discussion

Key findings

To the authors' knowledge, this is the first meta-analysis to investigate the prevalence of low bone mass and osteoporosis in patients with schizophrenia. Our meta-analysis indicates that patients with schizophrenia are almost twice as likely as age- and sex-matched controls to have low bone mass (OR=1.9, CI=1.3-2.7), a condition that affected approximately one in two patients (51%, CI= 43%-60%). We also found that approximately one in eight patients with schizophrenia had osteoporosis (13.2%, CI=7.8%-21.6%) and patients were over two and a half times more likely to have osteoporosis compared to the control populations (OR=2.86, CI=1.27-6.42). The pooled prevalence of osteopenia in patients with schizophrenia was 40.0% (CI=34.7%-45.4%) and was not statistically different to the comparison group (OR= 1.33, CI=0.93-1.90).

Our results build upon earlier narrative reviews (52). The findings of increased levels of low bone mass and in particular osteoporosis in schizophrenia patients is concerning given the consequences of fractures in this population (8, 9, 17, 18). Our systematic review identified only 19 eligible publications within the period from 2002-December 2013 (33-51) (Figure 1), indicating that the issue of bone health has been a low priority until relatively recently.

When considering bone health, identifying patients who currently have, or are at high risk for low bone mass is a clinical imperative. Knowledge about factors that are associated with low bone mass rates can help identify patients at greater risk. It is well established that people with schizophrenia typically have reduced levels of physical activity (13, 14, 53), poor diet (54), inadequate calcium intake, reduced levels of vitamin D and high levels of smoking (12) and these all likely contribute to the increased risk of low bone mass in schizophrenia. However, due to the paucity and inconsistency of the reporting of possible risk factors, the heterogeneity of populations, settings, and assessment methods, our moderator analyses did not enable us to clearly elucidate the mechanisms by which bone mass is decreased in people with schizophrenia. Surprisingly, we found inconsistent results in

our analyses regarding the influence of prolactin-raising antipsychotics and hyperprolactinemia. However, this is highly likely to be due to the heterogeneity and lack of studies providing accurate data on these important factors. We found interesting variations in the prevalence of low bone mass, with North America (35.3%, CI: 26.6-45.2%) having a particularly lower prevalence compared to Europe (53.6%, CI=38.0-68.5%) and Asia (58.4%, CI=48.4-67.7%), but there were no significant regional differences in osteoporosis and osteopenia. These geographic differences possibly suggest that protective factors, including genetic and environmental (lifestyle) effects, may play a role in modifying low bone mass risk in people with schizophrenia. It is established that the introduction of vitamin D fortified foods in the US has contributed to improved bone health in the general population (55) and this may have contributed to the lower prevalence of low bone mass even in high-risk groups, such as schizophrenia patients in the US. However, there was high heterogeneity in most of the subgroup analyses and these results should therefore be interpreted with caution. These results point to the fact that currently unmeasured moderator and mediator variables need to be assessed in future studies, such as diet and exercise, smoking frequency, cumulative time and dose of prolactin-raising and prolactin-neutral antipsychotic treatment, and pre-antipsychotic bone density measures. Moreover, once more studies are available, each providing data on the same and expanded set of moderator variables, multivariate regression analyses can be conducted that will further enhance the ability to examine the reasons for the heterogeneity of the findings.

Moreover, it is surprising that a higher BMI appeared to be a significant moderator of low bone mass while the converse is true in the general population (2, 4). The exact reasons for this finding are unclear, but this association may be attributable to a higher prevalence of unhealthy lifestyle factors (in particular sedentary behavior resulting in less bone re-modelling) and increased use of antipsychotic medications in individuals with a higher BMI. However, when applying a Bonferroni correction, this finding was not significant anymore.

Unsurprisingly, studies conducted in inpatient settings, where patients are likely to be in a more acute phase of illness and have restricted activity levels, had an increased prevalence of low bone mass compared to those in outpatient settings. Patients with schizophrenia are already less likely to receive adequate care for their reduced bone health (52), and inpatients appear to be most at risk for osteoporosis and receiving adequate care. Since we did not have any low bone mass data for drug-naïve people with schizophrenia relative to age- and sex-matched comparison subjects, it is not clear whether people with schizophrenia have a higher intrinsic vulnerability to low bone mass in the absence of medication.

Interestingly, in the exploratory meta-regression analyses, we found that a higher percentage of males were significantly associated with a higher prevalence of osteopenia and osteoporosis. Previous research demonstrated that risk of hip fracture is particularly elevated in male patients with schizophrenia (17) , and others (9) have speculated that this may be due to the fact that the onset of mental illness is earlier in males and crucially around a time when peak bone mass may not yet have been attained.

Clinical implications

We recommend that bone health assessments should form an integral part of the multidisciplinary treatment of schizophrenia. One clear way to identify those at risk is to measure a patient's skeletal status with QUS or BMD with DXA. DXA is the gold standard and is required to make a definitive diagnosis of osteoporosis, but is often inaccessible and impractical (56, 57). Although our results indicated that QUS underreported the prevalence of osteoporosis and osteopenia (but not of low bone mass), we believe this should be offered as a practical minimum. QUS is comparatively inexpensive, quick, easily transportable and does not emit radiation and results are highly correlated to DXA scans (48, 56-59). In addition, the United States preventative taskforce in their recommendation statement state that QUS of the calcaneus is as effective as DXA

in predicting future femoral neck, hip and vertebral fractures (60). Offering QUS assessments is particularly pertinent in inpatient settings where we found the highest prevalence of low bone mass, but also because it is an environment where access to a DXA scanner at a general hospital is much more difficult. However, it is essential that any patient identified as having low bone mass, osteoporosis or osteopenia with QUS should subsequently receive a central DXA scan (4) followed by appropriate intervention in case any pathological bone density loss is confirmed. In the United Kingdom, the National Osteoporosis Society states that individuals in the general population who have had a DXA scan should not need another one for at least two years (61). The European osteoporosis management guidelines (4) state that treatment for osteoporosis can be considered without a confirmatory DXA scan in environments where patients have limited access to densitometry. Therefore, patients with schizophrenia could possibly be considered for treatment under this category, especially if they had had a positive screen for osteoporosis with a QUS scan. The American College of Preventative Medicine report that DXA scan screening is cost effective in certain high risk populations (e.g. people over 70 years of age) but it remains unclear if this applies to people with schizophrenia (62). Currently, specific recommendations for the trigger points for and frequency of DXA screening for all people with schizophrenia or high risk subgroups cannot be made beyond the available recommendations for the general population. Future research is needed to determine if indications for and cost-effectiveness of osteoporosis screening in people with schizophrenia differ from the general population.

The prevention and treatment of low bone mass requires a multidisciplinary team approach involving psychiatrists, physicians, physical therapists, and other members who should educate and help motivate people with schizophrenia to improve their lifestyle. This should include effective lifestyle interventions, including smoking cessation, improved diet and exercise (7). Next to these, the treating psychiatrist should consider preferential use of or switching to a lower-risk medication (e.g. prolactin-sparing antipsychotic; (7)) or adding medication, such as bisphosphonates, selective

oestrogen receptor modulators and calcitonin to prevent or treat low bone mass (4, 7). Guidelines on the management of osteoporosis in general medicine from the United States (60) and Europe (4) recommend that management strategies include the promotion of physical activity. Research has consistently established that patients with schizophrenia are inactive (13), and our findings provide additional reasons for healthcare professionals to encourage patients to engage in more physical activity. Many osteoporotic fractures occur as a result of a falls, and physical activity is also effective in reducing the risk of falls (63), thus, providing a further imperative for promoting physical activity in patients with schizophrenia. Physical therapists can play a key role in promoting physical activity and also in the prevention of falls in this group.

Future research

Future research should prioritize the use of central DXA scans to measure BMD utilizing longitudinal designs. Future research should also examine whether low bone mass is moderated by genetic factors in addition to clinical characteristics. Within general medicine, there has been considerable emphasis on the development of lifestyle interventions to prevent osteoporosis. We believe it would be particularly pertinent to investigate the influence of physical activity upon bone mass in patients with schizophrenia. In particular, exercise plans should take into account the patient's risk of falls and include measures to reduce this risk. Future studies should prospectively examine the interaction between specific antipsychotics and prolactin levels and bone density, as well as the interaction with specific genotypes that could further moderate this risk.

Limitations

We wish to acknowledge several limitations in the primary data and our meta-analysis. First, considerable methodological heterogeneity was found across studies. In accordance with the MOOSE guidelines, we stratified the results in various subgroup analyses. Our results indicate that the heterogeneity, although expected, can only partly be controlled or explained by stratification for

osteoporosis and osteopenia, year of publication, treatment setting, sex, antipsychotic use, type of scan, methodological quality of the studies, and lifestyle factors. Since the heterogeneity often remained high in each subgroup analysis, the results should be interpreted with caution. Second, because our study findings were based on cross-sectional rather than longitudinal data, directionality of the association between the variables we investigated (including antipsychotic medication) and the observed low bone mass cannot be deduced with certainty. Third, a threat to the validity of any meta-analysis is publication bias. However, the Begg-Mazumdar and Egger's bias tests did not indicate any evidence of publication bias. Fourth, there was considerable inconsistency and heterogeneity in the reporting of risk factors for low bone mass and there were often missing data on duration of illness and duration of antipsychotic treatment, limiting the power for moderator analyses. In addition the moderator analyses should be considered as exploratory. Fifth, there were inadequate data on specific medications making it difficult to determine the influence of antipsychotic medications on the observed results. Sixth, only a few studies compared prevalence estimates in patients with schizophrenia with matched general population samples of the same region. Seventh, lifestyle behaviors were insufficiently recorded, precluding the meta-analytic assessment of these factors as moderating or mediating variables. Eighth, we pooled studies using T- and Z-scores obtained by DXA and QUS together and the accuracy of combining of DXA and QUS quantitative criteria have not been established. In addition, while QUS and DXA are highly correlated and QUS is as effective as DXA at predicting future fractures, they do provide different measures of bone structure. Finally, only five of the included studies were of high methodological quality. However, this is not completely unexpected as most studies did not have a control group and, consequently, such studies are expected to receive lower quality scores. Our categorical analyses demonstrated that there was no significant effect of study quality on the reported prevalence. Nevertheless, to our knowledge, this is the largest study of low bone mass prevalence figures in people with schizophrenia and the first formal meta-analysis of this important topic.

Conclusions

Our meta-analysis demonstrates that low bone mass affects more than half of the people with schizophrenia. Of greatest concern is the fact that osteoporosis is two and half times more common than in controls of a similar age and sex. In recognition of the possible adverse outcomes of fractures, multidisciplinary teams should routinely screen for and implement appropriate interventions targeting bone health. Future research should focus on evaluating modifiable risk factors and interventions that prevent bone mineral loss in people with schizophrenia.

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Conflict of Interest

Prof Dr De Hert has received consulting fees, speakers or advisory board fees, research support, or honoraria from AstraZeneca, Bristol- Myers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck JA, Pfizer, and Sanofi- Aventis.

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References

1. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med. 1993;**94**:646-50.
2. KANIS JA. Osteoporosis III: diagnosis of osteoporosis and assessment of fracture risk. Lancet. 2002;**359**:1929-36.
3. SURGEONS AAOO. Osteoporosis and bone health. [cited 27/11/2013]; Available from: http://www.aaos.org/news/aaosnow/may09/clinical8.asp
4. KANIS J, MCCLOSKEY E, JOHANSSON H, COOPER C, RIZZOLI R, REGINSTER JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporosis Int. 2013;**24**:23-57.
5. HALBREICH U. Osteoporosis, schizophrenia and antipsychotics: the need for a comprehensive multifactorial evaluation. CNS Drugs. 2007;**21**:641-57.
6. CREWS MPK, HOWES OD. Is antipsychotic treatment linked to low bone mineral density and osteoporosis? A review of the evidence and the clinical implications. Hum Psychopharmacol. 2012;**27**:15-23.
7. KISHIMOTO T, DE HERT M, CARLSON HE, MANU P, CORRELL CU. Osteoporosis and fracture risk in people with schizophrenia. Curr Opin Psychiatry. 2012;**25**:415-29.
8. HOLT RIG. Osteoporosis in people with severe mental illness: A forgotten condition. Maturitas. 2010;**67**:1-2.
9. JAVAID MK, I. G. HOLT R. Understanding osteoporosis. J Psychopharmacol. 2008;**22**:38-45.
10. STUBBS B. Antipsychotic-induced hyperprolactinaemia in patients with schizophrenia: Considerations in relation to bone mineral density. J Psychiatr Ment Health Nurs. 2009;**16**:838-42.
11. LAW MR, HACKSHAW AK. A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. BMJ. 1997;**315**:841-6.
12. FREEMAN TP, STONE JM, ORGAZ B, NORONHA LA, MINCHIN SL, CURRAN HV. Tobacco smoking in schizophrenia: investigating the role of incentive salience. Psychol Med. 2013:**1**,1-9.
13. VANCAMPFORT D, DE HERT M, DE HERDT A, et al. Associations between perceived neighbourhood environmental attributes and self-reported sitting time in patients with schizophrenia: A pilot study. Psychiatry Res. 2014;**215**:33-8.
14. VANCAMPFORT D, KNAPEN J, PROBST M, SCHEEWE T, REMANS S, DE HERT M. A systematic review of correlates of physical activity in patients with schizophrenia. Acta Psychiatr Scand. 2012;**125**:352-62.
15. CREWS M, LALLY J, GARDNER-SOOD P, et al. Vitamin D deficiency in first episode psychosis: A case–control study. Schizophr Res. 2013;**150**:533-7.
16. PEUSKENS J, PANI L, DETRAUX J, DE HERT M. The Effects of Novel and Newly Approved Antipsychotics on Serum Prolactin Levels: A Comprehensive Review. CNS Drugs. 2014. 28;**5**:421-53.
17. HOWARD L, KIRKWOOD G, LEESE M. Risk of hip fracture in patients with a history of schizophrenia. Br J Psychiatry. 2007;**190**:129-34.
18. SØRENSEN HJ, JENSEN SOW, NIELSEN J. Schizophrenia, antipsychotics and risk of hip fracture: A population-based analysis. Eur Neuropsychopharmacol. 2013;**23**:872-8.
19. JALBERT JJ, EATON CB, MILLER SC, LAPANE KL. Antipsychotic use and the risk of hip fracture among older adults afflicted with dementia. J Am Med Dir Assoc. 2010;**11**:120-7.
20. WU H, DENG L, ZHAO L, ZHAO J, LI L, CHEN J. Osteoporosis associated with antipsychotic treatment in schizophrenia. Int J Endocrinol. 2013;**2013**:167138.
21. MEYER JM, LEHMAN D. Bone Mineral Density in Male Schizophrenia Patients: A Review. Ann Clin Psychiatry. 2006;**18**:43-8.
22. STROUP DF, BERLIN JA, MORTON SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;**283**:2008-12.

23. MOHER D, LIBERATI A, TETZLAFF J, ALTMAN DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Clinical Trials. 2009;**6**:1-6.
24. WORLD HEALTH ORGANISATION. WHO SCIENTIFIC GROUP ON THE ASSESSMENT OF OSTEOPOROSIS AT PRIMARY HEALTH CARE LEVEL. WHO; [cited 01/12/2013]; Available from: http://www.who.int/chp/topics/Osteoporosis.pdf.
25. AMERICAN PSYCHIATRIC ASSOCIATION. Diagnostic and Statistical Manual of Mental Disorders – DSM-IV-TR. 4th edition. American Psychiatric Association; 2000.
26. WORLD HEALTH ORGANISATION. The ICD-10 Classification of Mental and Behavioural Disorders – Diagnostic Criteria for Research. 1993.
27. CHIN K-Y, IMA-NIRWANA S. Calcaneal quantitative ultrasound as a determinant of bone health status: what properties of bone does it reflect? Int J Med Sci. 2013;**10**:1778-83.
28. WELLS G, SHEA. B, O'CONNELL D, PETERSON JEA. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [cited 01/12/2013]; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
29. HEDGES LV, I O. Statistical models for meta-analysis. New York: Academic Press; 1985.
30. HIGGINS JPT, THOMPSON SG, DEEKS JJ, ALTMAN DG. Measuring inconsistency in meta-analyses. BMJ. 2003;**327**:557-60.
31. BEGG CB, MAZUMDAR M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;**50**:1088-101.
32. EGGER M, DAVEY SMITH G, SCHNEIDER M, MINDER C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;**315**:629-34.
33. DOKNIC M, MARIC NP, BRITVIC D, et al. Bone Remodelling, Bone Mass and Weight Gain in Patients with Stabilized Schizophrenia in Real-Life Conditions Treated with Long-Acting Injectable Risperidone. Neuroendocrinology. 2011;**94**:246-54.
34. HOWES O, SIMPSON L, MEANEY A, O'KEANE V, MURRAY R, AND, SMITH S. Are prolactin raising antipsychotics associated with osteoporosis? : J Psychopharmacology; 2002: **16**, 23.
35. HUMMER M, MALIK P, GASSER RW, et al. Osteoporosis in patients with schizophrenia. Am J Psychiatry. 2005;**162**:162-7.
36. JUNG D-U, CONLEY RR, KELLY DL, et al. Prevalence of bone mineral density loss in Korean patients with schizophrenia: A cross-sectional study. J Clin Psychiatry. 2006;**67**:1391-6.
37. JUNG D-U, KELLY DL, OH M-K, et al. Bone mineral density and osteoporosis risk in older patients with schizophrenia. J Clin Psychopharmacol. 2011;**31**:406-10.
38. KINON BJ, LIU-SEIFERT H, STAUFFER VL, JACOB J. Bone Loss Associated with Hyperprolactinemia in Patients with Schizophrenia. Clin Schizophr Relat Psychoses. 2013;**7**:115-23.
39. KISHIMOTO T, WATANABE K, TAKEUCHI H, et al. Bone mineral density measurement in female inpatients with schizophrenia. Schizophr Res 2005.;**77**:113-5.
40. KISHIMOTO T, WATANABE K, SHIMADA N, MAKITA K, YAGI G, KASHIMA H. Antipsychotic-induced hyperprolactinemia inhibits the hypothalamo-pituitary-gonadal axis and reduces bone mineral density in male patients with schizophrenia. J Clin Psychiatry. 2008;**69**:385-91.
41. LIN C-H, HUANG K-H, CHANG Y-C, et al. Clozapine protects bone mineral density in female patients with schizophrenia. Int J Neuropsychopharmacol. 2012;**15**:897-906.
42. LEHMAN D, MEYER JM. Decreased bone mineral density in male schizophrenia patients. Schizophr Res. 2005;**76**:131-3.
43. LIU-SEIFERT H, KINON BJ, AHL J, LAMBERSON S. Osteopenia associated with increased prolactin and aging in psychiatric patients treated with prolactin-elevating antipsychotics. Ann N Y Acad Sci. 2004;**1032**:297-8.
44. MARIC N, POPOVIC V, JASOVIC-GASIC M, PILIPOVIC N, VAN OS J. Cumulative exposure to estrogen and psychosis: a peak bone mass, case-control study in first-episode psychosis. Schizophr Res. 2005;**73**:351-5.

45. MEANEY AM, SMITH S, HOWES OD, O'BRIEN M, MURRAY RM, O'KEANE V. Effects of long-term prolactin-raising antipsychotic medication on bone mineral density in patients with schizophrenia. Br J Psychiatry. 2004;**184**:503-8.
46. O'KEANE V, MEANEY AM. Antipsychotic Drugs: A New Risk Factor for Osteoporosis in Young Women With Schizophrenia? J Clin Psychopharmacol. 2005;**25**:26-31.
47. RANJBAR F, FARJAMFAR M, ALIASGARZADEH A, ALIZADEH M. P03-110 - The evaluation of bone mineral density and osteoporosis in schizophrenic patients. Eur Psychiatry supp. 2010;**25**:1090.
48. JENN-HUEI R, NAN-PING Y, CHING-MO C, CHIH-YUAN L, TSUO-HUNG L, PESUS C. Bone mass in schizophrenia and normal populations across different decades of life. BMC Musculoskelet Disord. 2009;**10**:1-7.
49. STUBBS B, ZAPATA-BRAVO E, HAW C. Screening for osteoporosis: a survey of older psychiatric inpatients at a tertiary referral centre. Int Psychogeriatr. 2009;**21**:180-6.
50. SUGAWARA N, YASUI-FURUKORI N, UMEDA T, et al. Effect of age and disease on bone mass in Japanese patients with schizophrenia. Ann Gen Psychiatry. 2012;**11**:5.
51. VAN DER LEEUW C, HABETS P, DOMEN P, VAN KROONENBURGH M, VAN OS J, MARCELIS M. Bone mineral density as a marker of cumulative endogenous estrogen exposure: Relationship to background genetic risk of psychotic disorder. Schizophr Res. 2013;**143**:25-31.
52. LEUCHT S, BURKARD T, HENDERSON J, MAJ M, SARTORIOUS N. Physical illness and schizophrenia: a review of the literature. Acta Psychiatr Scand. 2007. **116**:317-3.
53. VANCAMPFORT D, PROBST M, SCHEEWE T, KNAPEN J, DE HERDT A, DE HERT M. The functional exercise capacity is correlated with global functioning in patients with schizophrenia. Acta Psychiatr Scand. 2012;**125**:382-7.
54. DIPASQUALE S, PARIANTE CM, DAZZAN P, AGUGLIA E, MCGUIRE P, MONDELLI V. The dietary pattern of patients with schizophrenia: A systematic review. J Psychiatr Res. 2013;**47**:197-207.
55. CALVO MS, WHITING SJ, BARTON CN. Vitamin D fortification in the United States and Canada: current status and data needs... Am J Clin Nutr. 2004;**80** (Suppl):1710S-6S.
56. LIU H, PAIGE NM, GOLDZWEIG CL, et al. Screening for osteoporosis in men: a systematic review for an American College of Physicians guideline. Ann Intern Med. 2008;**9**, 148:685.
57. BABATUNDE OO, FORSYTH JJ. Quantitative Ultrasound and bone's response to exercise: A meta analysis. BONE. 2013;**53**:311-8.
58. BAUER DC, EWING SK, CAULEY JA, ENSRUD KE, CUMMINGS SR, ORWOLL ES. Quantitative ultrasound predicts hip and non-spine fracture in men: the MrOS study. Osteoporos Int. 2007;**18**:771-7.
59. PARTTI K, HELIÖVAARA M, IMPIVAARA O, et al. Skeletal status in psychotic disorders: a population-based study. Psychosom Med. 2010;**72**:933-40.
60. Screening for Osteoporosis: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2011;**154**:356-W119.
61. NATIONAL OSTEOPOROSIS S SOCIETY. Osteoporosis sources for primary care. [cited 01/04/2014]; Available from: http://www.osteoporosis-resources.org.uk/investigation/8-how-should-gps-use-bone-densitometry.
62. LIM LS, HOEKSEMA LJ, SHERIN K. Screening for osteoporosis in the adult U.S. population: ACPM position statement on preventive practice. Am J Prev Med. 2009;**36**:366-75.
63. SHERRINGTON C, WHITNEY JC, LORD SR, HERBERT RD, CUMMING RG, CLOSE JCT. Effective exercise for the prevention of falls: a systematic review and meta-analysis. J Am Geriatr Soc. 2008;**56**:2234-43.

Table 1. Summary of included studies

Study/ Reference Number	Design and setting	Schizophrenia participants N, % male, Age and population details	Diagnostic criteria	Other details Other details (Duration of illness, duration of antipsychotic treatment, type of antipsychotic, lifestyle factors,	Controls N, % male, Age	NOS score	Type of bone scan & measurement	Number (%) patients with schizophrenia with low bone mass, osteoporosis and osteopenia	Number (%) controls with schizophrenia with low bone mass, osteoporosis and osteopenia
33	Serbia Cross sectional Out-patients	N=26 31.3±1.1 years 12 (50%) male All outpatients with well-controlled schizophrenia without any other psychiatric comorbidity.	DSM IV	BMI 28.2 ±1.0 Duration of schizophrenia 7.7 ±1.1 years Duration of AP 6.9±1.0 years Smokers: Schizophrenia 46%, controls 20% p=0.02 Regular menstrual cycles: Schizophrenia 86%, controls 92% PNSS 76.0±2.9 All on risperidone 18.0±1.6 months Physical activity Serum 25(OH)D nmol/ l: Schizophrenia 23.6, controls 71.9 (p<0.001) Osteocalcin ng/ml: Schizophrenia 18.0, controls 16.1	35 health controls Matched age, gender and BMI 32.2±1.4 years 12 males	6	DXA Z score Lx spine	*Low bone mass:* Total 14 (53.8%) *Osteoporosis:* Total 3 (11.5%) *Osteopenia*: Total 11 (42.3%)	*Low bone mass:* Total 10 (28.5%) *Osteoporosis:* Total 2 (5.7%) *Osteopenia*: Total 8 (22.8%)
34	UK Cross sectional Out-patients	N= 48 46.6±12.3 years 24 (50%) male Consecutive outpatients invited to participate in the study	ICD 10	All patients on long term antipsychotic medication ? length	No control group	3	DXA T score Lx spine	*Low bone mass:* Total 32 (66.7%) *Osteoporosis:* Total 4 (8.3%) *Osteopenia*: 28 (58.3%)	N/A

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Study/ Reference Number	Design and setting	Schizophrenia participants N, % male, Age and population details	Diagnostic criteria	Other details Other details (Duration of illness, duration of antipsychotic treatment, type of antipsychotic, lifestyle factors,	Controls N, % male, Age	NOS score	Type of bone scan & measurement	Number (%) patients with schizophrenia with low bone mass, osteoporosis and osteopenia	Number (%) controls with schizophrenia with low bone mass, osteoporosis and osteopenia
35	Cross sectional USA Mixed in- and out-patients	N=75 34.8±6.2 years 57 males (76%) 33.6±5.4 years 18 females 38.3±7.4 years In- and outpatients invited to take part in the study.	ICD 10	All receiving AP >1 year BMI total sample 27.6±5.4 Males = 27.5±4.9, females 27.7 ±6.7 Duration of illness: Total sample 118.0±83.5 Male 117.0±77.3 months Females 121.2±103.0 months PNSS scores total sample 62.2 ±21.3 Males 61.4±21.2, females 64.8±21.8 52 (69.3%) smokers Non PR AP medication: 45 (78.9%) males and 13 (72.2%) females PR AP medication 10 (17.5%) males and 4 (22.2%) females	No control group.	4	DXA T score Lx spine	<u>*Low bone mass*</u>*:* Total 38 (50.6%) <u>*Osteoporosis*</u>*:* Total: 6 (8%) <u>*Osteopenia*</u>: Total 32 (42.6%)	N/A
36	Cross sectional Korea	N=51 30 (58.8%) males 39.9 ±5.1 years	DSM IV	All taken haloperidol for >2 years, mean duration of treatment Males 89.5 ±59.5 months Females 84.5 ±62.2 months BMI: Males 23.9 ±5.6	57 healthy controls 40.3±3.3 years female 36.9±6.5years male	6	DXA T score Lx spine Femoral	<u>*Low bone mass*</u>*:* Total 33 (64.7%) <u>*Osteoporosis*</u>*:* Total 6 (11.8%)	<u>*Low bone mass*</u>*:* Total 25 (43.8%) <u>*Osteoporosis*</u>*:* Total 4 (7%)

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Study/ Reference Number	Design and setting	Schizophrenia participants N, % male, Age and population details	Diagnostic criteria	Other details Other details (Duration of illness, duration of antipsychotic treatment, type of antipsychotic, lifestyle factors,	Controls N, % male, Age	NOS score	Type of bone scan & measurement	Number (%) patients with schizophrenia with low bone mass, osteoporosis and osteopenia	Number (%) controls with schizophrenia with low bone mass, osteoporosis and osteopenia
		21 females (41.2%) 37.8 ±5.5 years All patients clinically stable.		Females 23.5 ±3.4 Smokers: Males 15 (50%) 0 females 17 (80.9%) of females had amenorrhea	BMI: Males 24.1 ±4.8 Females 22.±8 4.9 Smokers: 13 (38.2%) males and 0 females		neck and trochanter	*Osteopenia*: Total 27 (52.9%)	*Osteopenia*: Total 21 (36.8%)
37	Cross sectional Korea In-patients	N=229 136 (59.4%) males 58.2±5.7 years 93 females (40.6%) 59.1±7.8 years All clinically stable on current medication for 1 year.	DSM IV	All 50 years and older 100% females postmenopausal BMI: Males 23.1±3.5 Females 22.3±3.8 Duration of illness: Males 135.3± 77.9 months Females 149.0± 82.0 months Smokers total sample: 88 (38.4%) Fracture history total sample: 55 (24.0%) Alcohol dependence diagnosis: 45 (33.1%) males 8 (8.6%) AP medication 206 (89.9%) taking first generation	125 healthy volunteers 65 males & 60 females 59.0 ±6.8 years males 58.2 ± 6.0 years females BMI: Females 22.5±2.4 Males 21.9±2.8 Smokers: 11 (8.8%) Fracture history:	6	DXA T score Lx spine Femur neck & trochanter	*Low bone mass:* Total 183 (79.9%) *Osteoporosis:* Total 80 (34.9%) *Osteopenia*: Total 103 (45.0%)	*Low bone mass:* Total 83 (66.4%) *Osteoporosis:* Total 23 (18.4%) *Osteopenia*: Total 60 (48%)

Table 1. Summary of included studies

Study/ Reference Number	Design and setting	Schizophrenia participants N, % male, Age and population details	Diagnostic criteria	Other details Other details (Duration of illness, duration of antipsychotic treatment, type of antipsychotic, lifestyle factors,	Controls N, % male, Age	NOS score	Type of bone scan & measure ment	Number (%) patients with schizophrenia with low bone mass, osteoporosis and osteopenia	Number (%) controls with schizophrenia with low bone mass, osteoporosis and osteopenia
				23 (10.0%) taking second generation	7 (5.6%)				
38	Cross sectional USA Mixed in- and out-patients	N=402 255 (63.4%) males 40.8 ±10.0 years 147 females 44.5 ±11.4 years Participants attended 1 of 27 centres across the USA. Post hoc analysis of large open label trial.	DSM IV schizophrenia and schizo-affective disorder	Average AP treatment (all drugs) >8±5.8 years Menopausal status 51 (34.7%) post-menopausal Hyperprolactinaemia: 110 (43%) males 90 (31%) females	No control group.	4	QUS T scores Calcaneus	*Low bone mass:* Total 110 (27.6%) *Osteoporosis:* Total 8 (1.9%) *Osteopenia*: Total 102 (25.4%)	N/A
39	Cross sectional Japan In-patients	N=133 100% female 55.4±15.9 years All inpatients and able to	DSM-IV schizophrenia / schizo-affective disorder	All had no conditions affecting BMD	No control group.	4	QUS T score Calcaneus	*Low bone mass:* N/A *Osteoporosis:* Total 78 (58.6%)	N/A

Table 1. Summary of included studies

Study/ Reference Number	Design and setting	Schizophrenia participants N, % male, Age and population details	Diagnostic criteria	Other details Other details (Duration of illness, duration of antipsychotic treatment, type of antipsychotic, lifestyle factors,	Controls N, % male, Age	NOS score	Type of bone scan & measurement	Number (%) patients with schizophrenia with low bone mass, osteoporosis and osteopenia	Number (%) controls with schizophrenia with low bone mass, osteoporosis and osteopenia
		perform certain level of activities of daily living.						*Osteopenia*: N/A	
40	Cross sectional Japan In-patients	N= 74 100% male 58.9±12.2 years All hospitalised and free from comorbidities that may influence BMD.	DSMI IV	Durations of illness 34.6±13.0 years Treatment duration 34.6 years±14.8 years 37 (50%) smokers Physical activity (pedometer steps per day, n=63): 27 (<5,000 steps), 20 (5,000-9,999 steps) and 16 (10,000 steps). 87% hyperproaclintainaemic	No control group.	4	DXA T score Distal radius	*Low bone mass:* Total 48 (64.8%) *Osteoporosis:* Total 20 (27%) *Osteopenia*: Total 28 (37.8%)	N/A
41	Cross sectional Taiwan In-patients	N=48, 100% female 24 taking prolactin raising (PR) antipsychotics 41.8±8 years 24 taking clozapine, 41.7±10.2 years	DSM IV	PR BMI 25.3±4.1 Clozapine BMI 25.7±4.1 Duration of disease: PR group 245.5±130 months Clozapine 255.6±108.9 months Duration hospitalisation: PR group 683.3±546.1 months Clozapine 944.2±763.9 months PANSS total score: PR 77.8±17.6 Clozapine 87.2±19.3 Physical activity (Pedometer steps	No control group.	4	DXA T score Lx spine	*Low bone mass:* Total 15 (31.2%) *Osteoporosis:* Total 1 (2.1%) *Osteopenia*: Total 14 (29.2%)	N/A

Table 1. Summary of included studies

Study/ Reference Number	Design and setting	Schizophrenia participants N, % male, Age and population details	Diagnostic criteria	Other details Other details (Duration of illness, duration of antipsychotic treatment, type of antipsychotic, lifestyle factors,	Controls N, % male, Age	NOS score	Type of bone scan & measurement	Number (%) patients with schizophrenia with low bone mass, osteoporosis and osteopenia	Number (%) controls with schizophrenia with low bone mass, osteoporosis and osteopenia
		All with chronic schizophrenia and hospitalised for ≥6 months.		per day) PR 6593.2±6287 Clozapine 4944.9±4138.2 Post-menopausal: PR 3 (12.5%) Clozapine 4 (16.7%) Hyperpractinaemia: PR group 23 (95.8%) Clozapine 5 (20.8%)					
42	Cross sectional USA ? setting	N= 10 100% male 48.1±6.5 years All with chronic schizophrenia	? criteria Schizophrenia / schizo-affective disorder	100% smokers p=0.037 difference to controls BMI 30.4 ±6.4 ns difference to controls	10 age and gender matched controls 100% male, had treatment for depression and/ or post-traumatic stress disorder	4	DXA T score Unclear	<u>*Low bone mass*</u>*:* Total 4 (40%) <u>*Osteoporosis*</u>*:* Total 1 (10%) <u>*Osteopenia*</u>: Total 3 (30%)	<u>*Low bone mass*</u>*:* Total 0 <u>*Osteoporosis*</u>*:* Total 0 <u>*Osteopenia*</u>: Total 0
43	Cross sectional Community USA	N= 384 248 males (64.5%) All treated in	? criteria Schizophrenia	All taking conventional PR antipsychotics medication or atypical risperidone.	N/A	3	QUS T score	<u>*Low bone mass*</u>*:* Total 111 (28.9%) <u>*Osteoporosis*</u>*:*	N/A

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Study/ Reference Number	Design and setting	Schizophrenia participants N, % male, Age and population details	Diagnostic criteria	Other details Other details (Duration of illness, duration of antipsychotic treatment, type of antipsychotic, lifestyle factors,	Controls N, % male, Age	NOS score	Type of bone scan & measurement	Number (%) patients with schizophrenia with low bone mass, osteoporosis and osteopenia	Number (%) controls with schizophrenia with low bone mass, osteoporosis and osteopenia
	Out-patients	the community for >3 months		Excluded those taking prolactin sparring antipsychotic medication (quetiapine, olanzapine, or clozapine)			Calcaneus	N/A *Osteopenia*: N/A	
44	Cross sectional Serbia ? setting	N=19 100% female 24.5±3.8 years All females recruited as soon as possible after presenting in a first episode.	DSM IV schizophrenia or schizophreni-form disorder	All first episode psychosis Education secondary/ higher degree=80%/20% 11 (57.9%) smokers BMI 22.8	20 healthy controls 100% female matched for age 23.7±3.1 years and education secondary/higher degree=84%/16%, (p=0.73) BMI 21.0	6	DXA Lx spine (L1-4)	*Low bone mass:* Total 4 (21%) *Osteoporosis:* Total 0 *Osteopenia*: Total 4 (21%)	*Low bone mass:* Total 1 (5%) *Osteoporosis:* Total 0 *Osteopenia*: Total 1 (5%)
45	Cross sectional Ireland and UK Out-patients	N= 55 30 male (54.5%) 43.5±11.4 years 25 females 59±5.5 years All females	DSM IV Schizophrenia	All treated on prolactin raising antipsychotic medication >10 years BMI: 28.0 ±4.4 male 30.3 ±4.6 female Treatment duration 16±7.7 years male group 21±5.5 years female group	N/A	4	DXA Z score Lx spine Left femoral neck, trochante	*Low bone mass:* Total 42 (76.4%) *Osteoporosis:* Total 11 (20%) *Osteopenia*: Total 31 (56.4%)	N/A

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Study/ Reference Number	Design and setting	Schizophrenia participants N, % male, Age and population details	Diagnostic criteria	Other details Other details (Duration of illness, duration of antipsychotic treatment, type of antipsychotic, lifestyle factors,	Controls N, % male, Age	NOS score	Type of bone scan & measurement	Number (%) patients with schizophrenia with low bone mass, osteoporosis and osteopenia	Number (%) controls with schizophrenia with low bone mass, osteoporosis and osteopenia
		post-menopausal 46 (83.6%) Caucasian Recruited from 3 sites, 2 in Ireland and 1 in UK, all treated in the community.		Daily exercise: 40.3±34.4 min/day Male group 19.2±15.7 min/ day female group BRPS: 12.2 ±12.7 Male 12.4 ±17.4 female			ric region		
46	Cross sectional Ireland Out-patients	N=38 100% female 26 taking prolactin raising antipsychotic medication 32.8 ±6.8 years 12 prolactin sparring medication 29.5 ±5.7 years All outpatients recruited from Ireland.	DSM IV	All pre-menopausal women receiving antipsychotic medication for > 1 year PR group: BMI 28 ±4.5 Treatment duration 8.4 ±4.7 years Exercise 193.1 ±113 min per week SANSS 12.7 ±19.1 BRPS 5.9 ±5.9 25 (96%) hyperprolactimaemia Prolactin sparring group: BMI 27 ±3 Treatment duration 6.3 ±3.8 years Exercise 175.8 ±95.7 min per week SANSS 12.3 ±17 BRPS 4 ±6.6	No control group.	4	DXA Z score Lx spine Femoral neck and trochanteric region	*Low bone mass:* Total 19 (50%) *Osteoporosis:* Total 4 (10.5%) *Osteopenia*: Total 15 (39.5%)	N/A

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Study/ Reference Number	Design and setting	Schizophrenia participants N, % male, Age and population details	Diagnostic criteria	Other details Other details (Duration of illness, duration of antipsychotic treatment, type of antipsychotic, lifestyle factors,	Controls N, % male, Age	NOS score	Type of bone scan & measurement	Number (%) patients with schizophrenia with low bone mass, osteoporosis and osteopenia	Number (%) controls with schizophrenia with low bone mass, osteoporosis and osteopenia
				4 (33%) hyperprolactinaemia					
47	Cross sectional Iran ? setting	N=85 68 (80%) males 39.61± 6.77 years 17 females (20%) 36.29± 7.58 years	?	N/A	No control group.	3	DXA T score Lx spine	*Low bone mass:* Total 46 (54%) *Osteoporosis:* Total 12 (14.1%) *Osteopenia*: Total 34 (40%)	N/A
48	Cross sectional Taiwan Inpatients	N=965 623 male (64.5%) 47.6±15.9 years 342 females 46.81±1.2 years All patients with chronic schizophrenia.	DSM IV	n/a	N=405 local community 54.2 ± 16.0 years 183 (45%) male 60.0 ± 18.2 years 222 (55%) female Not matched on age and gender	4	QUS T score Calcaneus	*Low bone mass:* Total 570 (59.0%) *Osteoporosis:* Total 129 (13.4%) *Osteopenia*: Total 441 (45.7%)	*Low bone mass:* Total 283 (69.8%) *Osteoporosis:* Total 71 (17.5%) *Osteopenia*: Total 212 (52.5%)
49	Cross sectional UK	N= 21 71.0 ±10.6	DSM IV	On PR AP: 17 (80.9%) History of fractures 7 (33.3%)	No control group.	3	DXA T score	*Low bone mass:* Total 15 (71.4%)	N/A

Table 1. Summary of included studies

Study/ Reference Number	Design and setting	Schizophrenia participants N, % male, Age and population details	Diagnostic criteria	Other details Other details (Duration of illness, duration of antipsychotic treatment, type of antipsychotic, lifestyle factors,	Controls N, % male, Age	NOS score	Type of bone scan & measurement	Number (%) patients with schizophrenia with low bone mass, osteoporosis and osteopenia	Number (%) controls with schizophrenia with low bone mass, osteoporosis and osteopenia
	Inpatients	16 male (76.6%) 5 female (23.3%) All long-stay inpatients with chronic schizophrenia.					Radius	*Osteoporosis:* Total 14 (66.67%) *Osteopenia*: Total 1 (4.7%)	
50	Cross sectional Japan Inpatients	N=362 178 males (49.1%) 48.0 ± 14.9 years 184 females 49.7 ± 15.9 years Data collected from 3 hospitals.	DSM IV schizophrenia or schizo-affective disorder	n/a	832 healthy volunteers 327 males (39.3%) 56.0 ± 13.8 years 505 females 58.1 ± 13.0 years	4	QUS T score Calcaneus	*Low bone mass:* Total 172 (47.5%) *Osteoporosis:* Total 13 (3.6%) *Osteopenia*: Total 159 (43.9%)	*Low bone mass:* Total 353 (42.4%) *Osteoporosis:* Total 1 (0.1%) *Osteopenia*: Total 352 (42.3%)
51	Cross sectional Netherlands and Belgium	N=49 28.1 years 39 male (79.5%) 10 female	DSM IV	No demographic information on schizophrenia patients.	N=48 27.42±6.39 years	7	DXA T SCORE Lumbar	*Low bone mass:* Total 15 (30.6%) *Osteoporosis:* Total 1 (2.0%)	*Low bone mass:* Total 10 (20.8%) *Osteoporosis:* Total 1 (2.0%)

Table 1. Summary of included studies

Study/ Reference Number	Design and setting	Schizophrenia participants N, % male, Age and population details	Diagnostic criteria	Other details Other details (Duration of illness, duration of antipsychotic treatment, type of antipsychotic, lifestyle factors,	Controls N, % male, Age	NOS score	Type of bone scan & measurement	Number (%) patients with schizophrenia with low bone mass, osteoporosis and osteopenia	Number (%) controls with schizophrenia with low bone mass, osteoporosis and osteopenia
	Mixed setting	Consecutive in- or outpatients from a larger longitudinal study					spine	*Osteopenia*: Total 14 (28.6%)	*Osteopenia*: Total 9 (18.75%)

Key: NOS = Newcastle Ottawa Scale score, N/A = not available, USA=United States of America, N=Number, PR= prolactin raising, AP=antipsychotic, BMI=body mass index, QUS = quantitative ultrasound, DXA= dual-energy X-ray absorptiometry, N/A= not available

Table 2 Pooled and subgroup prevalence of low bone mass in people with schizophrenia

		N	*Prevalence (95% CI)*	*Q-value*	*df (Q)*	*P-value*	*I-squared %*
Overall pooled prevalence of low bone mass		2905	51.7% (43-60)	274.67	17	<0.0001	93.8
Moderator Variable	**Subgroup**						
Region	North America	835	35.3% (26.6-45.2)	15.62	3	0.001	80.8
	Europe	256	53.6% (38.0-68.5)	32.68	6	<0.0001	81.6
	Asia	1814	58.4% (48.4-67.7)	73.27	6	<0.0001	91.8
Prolactin Raising antipsychotic medication	Yes	757	63.1% (40.3-81.2)	134.0	5	<0.0001	96.2
	Mixed	593	46.7% (30.0-64.2)	49.85	5	<0.0001	89.9
	Unclear	1555	47.2% (38.6-55.9)	33.13	5	<0.0001	84.9
Type of Bone Scan	DXA	828	55.4% (45.1-65.3)	91.0	13	<0.0001	85.7
	QUS	2077	41.0% (26.5-57.2)	144.7	3	<0.0001	97.9
Definition of low bone mass	T score	2786	49.5% (39.5-59.6)	260.6	13	<0.0001	95.0
	Z score	119	61.1% (42.4-77.1)	7.63	2	0.02	73.8
Setting of study	Inpatient	1750	60.3% (49.6-70.1)	74.0	6	<0.0001	91.89
	Outpatient	525	53.7% (35.6-70.9)	50.02	5	<0.0001	90.0
	Mixed	630	32.9% (21.6-46.7)	16.1	3	0.001	81.43
Methodological quality	High	374	51.4% (28.0-74.1)	55.92	4	<0.0001	92.84
	Med/ low	2531	51.6% (39.9-63.0)	117.47	12	<0.0001	91.9

Key: N=number of patients with schizophrenia