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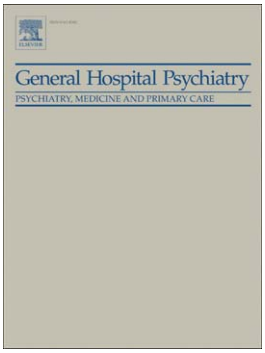

Schizophrenia and the risk of fractures: A systematic review and comparative meta-analysis

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Schizophrenia and the risk of fractures: A systematic review and comparative meta-analysis

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Abstract

Background

People with schizophrenia experience increased rates of osteoporosis and may be at heightened risk of fractures. We conducted a systematic review and meta-analysis to investigate fractures among people with schizophrenia compared to people without mental illness.

Method

We systematically searched major electronic databases from inception till 10/2014. Articles were included that reported the number of fractures in people with schizophrenia and a control group. Two independent authors conducted searches, completed methodological assessment and extracted data. Data was narratively synthesised and a random effects incidence rate ratio (IRR) meta-analysis was performed.

Results

Eight studies were included encompassing 48,384 people with schizophrenia (49.9 -75.2 years, 41-100% female) and 3,945,783 controls. The pooled adjusted rate of fractures per 1000 person years was 5.54 (95% CI 4.92-5.57) in people with schizophrenia and 3.48 (95% CI 3.39-3.64) in control participants. The comparative meta-analysis showed that people with schizophrenia experience rate of fractures compared to control participants (IRR 1.72, 95% CI = 1.24 to 2.39, I^2=49%; n= 168,914). There was insufficient data to conduct a robust moderator analysis, but the narrative review consistently highlighted antipsychotic medication was an important risk factor for fractures.

Conclusion

People with schizophrenia are at significantly increased risk of fractures. Future research is required to understand the mechanisms and should seek to validate fracture prediction algorithms used in the general population. Importantly there is a need to develop preventative strategies to improve

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bone health and reduce fracture risk involving the wider multidisciplinary team and incorporating falls prevention strategies.

Key words: schizophrenia, psychosis, fracture, osteoporosis, fragility fracture

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Introduction

Osteoporosis and associated fractures are a significant public health concern because of related mortality, morbidity, disability, and diminished quality of life [1,2]. Although osteoporosis is often referred to as the 'silent disease' it is highly clinically relevant due to the drastically increased risk of fractures which often occur as a consequence of the condition [1,2]. People with schizophrenia experience poorer physical health outcomes including reduced bone mineral density [3-6], with a recent systematic review establishing that people with schizophrenia are two and a half times more likely to have osteoporosis than people of similar age and sex without mental illness [7].

There are a multitude of complex reasons why people with schizophrenia may be at increased risk of fractures. For instance, people with schizophrenia typically take antipsychotic and other psychotropic medication which is associated with antipsychotic induced hyperprolactinaemia and osteoporosis [5] and falls [8,9] which are a leading cause of fracture due to trauma. Moreover, people with schizophrenia engage in lower levels of physical activity [10], have reduced lower limb strength [11] and may experience high levels of pain [12] which are important risk factors for falls [13,14] and therefore increase the risk of fracture. In addition, people with schizophrenia are at greatly increased risk of diabetes [15,16] which is a key risk factor for fractures in the general population [17]. Some vulnerability for falling and fractures may derive from the illness itself since children who later go on to develop schizophrenia are noted to have more motor coordination difficulties than their peers [18,19]. Furthermore, alcohol use disorder is common in people with schizophrenia [6] and this may also increase risk of falling and subsequent fracture. Other potential risk factors that may also increase the risk of fractures include increased levels of stress hormones such as cortisol [20-22].

It is particularly important to determine if there is a relationship between schizophrenia and fractures as research in general medicine has consistently established increased levels of mortality following fractures [23]. In addition, fractures in people with serious mental illnesses (SMI) such as schizophrenia can also lead to a deterioration of mental state [24], higher post-operative infection

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rates, worse ambulatory rates after one year, and a risk of contralateral fractures [25]. Unfortunately, complications are more likely to arise in this group. A recent large study investigating 10,669,449 lower limb fractures [26] established that patients with schizophrenia (0.6% of the sample) spent more time in hospital post fracture (11 days) than any other patient group, including other groups such as dementia where there has been an increased effort to reduce fractures. In addition, Menendez et al [26] found that patients with schizophrenia experience significantly more adverse events following hip fractures including pneumonia, acute renal failure and deep venous thrombosis compared to those without mental illness (OR, 1.2; 95% CI, 1.2–1.3; $p<0.001$).

Previously, a number of meta-analyses have reported that antipsychotic medication use is associated with an increased risk of fractures in older people [8,27]. A selective narrative review in people with schizophrenia also indicated that osteoporotic fractures may have considerable adverse effects on general health, subjective well-being, the ability to engage in healthy lifestyle behaviors, and increased healthcare costs [9]. However, to date, no systematic review or meta-analysis has specifically investigated the relationship between schizophrenia and fractures. This is warranted in order to provide a rigorous up-to-date risk profile and inform relevant policy in this area. Therefore, we conducted a systematic review and meta-analysis to investigate the association between schizophrenia and fractures.

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Method

This systematic review was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines [28] and reported in accordance with the PRISMA statement [29] following a predetermined but unpublished protocol.

Inclusion and exclusion criteria

We included observational studies (prospective, retrospective or cross-sectional) that: (a) included people with a diagnosis of schizophrenia according to recognised criteria (DSM V [30] or ICD 10[31]) together with a control group of people without a mental illness, and (b) reported the number of fractures over any period of time. We also included observational studies that reported the number of people with schizophrenia in comparative studies containing groups with and without a fracture. If we included mixed samples (e.g. pooled sample of SMI) we attempted to extract the schizophrenia specific data. If this was not possible we contacted the authors up to two times over a one month period to obtain the schizophrenia specific data. If we received no response and the study included ≥80% with a diagnosis of schizophrenia we included the data. Due to the anticipated paucity of research, we collected data on any type and body site for the fracture that was confirmed through radiographs, medical note review or self-report. We did not place any language restrictions upon our searches. When we encountered studies reporting data from the same sample at different time points, we used the most recent data and/or the largest data set.

Information sources and searches

Two independent reviewers searched Academic Search Premier, MEDLINE, Psychology and Behavioral Sciences Collection, PsycINFO, SPORTDiscus, CINAHL Plus and Pubmed from inception until October 2014. We used the key words 'schizophrenia' or 'schiz*' or 'psychosis' and 'fracture*' or 'osteoporosis'. In addition, the reference lists of all eligible articles and recent systematic reviews

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on bone health in people with schizophrenia were considered [7,9]. Primary/corresponding authors of research groups were contacted where necessary.

Study Selection

After the removal of duplicates, two independent reviewers screened the titles and abstracts of all potentially eligible articles. Both authors applied the eligibility criteria, and a list of full text articles was developed through consensus. The two reviewers then considered the full texts of these articles and the final list of included articles was reached through consensus.

Data Extraction

Two authors independently extracted data in a predetermined database. The data collected from each article included: study design, geographical location, details of schizophrenia participants (mean age, % males, diagnosis method, details of medications and chronicity of illness, and comparison group participant characteristics (mean age, % males)). We extracted data on fractures within the studies including the body site, method of acquiring the data, duration of data collection and details regarding the circumstances that contributed to fractures (e.g. falls, accidents).

Methodological quality assessment

Two authors completed methodological quality assessment of included articles using the Newcastle Ottawa Scale (NOS; [32]). The NOS is utilized to assess the methodological quality of non-randomized trials and has acceptable validity and reliability [32]. The assessment tool focuses on three main methodological features: (1) the selection of the groups, (2) the comparability of the groups and (3) the ascertainment of the outcome of interest. Studies were given a NOS score ranging from 0-9, with a score of 5 or greater indicative of satisfactory methodological quality.

Data analysis

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The results from the included studies were reported in a narrative synthesis and also a meta-analysis in accordance with the Cochrane reviewer's handbook [33]. Where possible we extracted raw data from the studies (or utilised data provided from authors upon request) regarding the number of people with and without a fracture in the schizophrenia and control groups. We then corrected for years of observation and sample size (i.e. person-years of observation) to compare the incidence rates (IR) of fractures across studies of differing time points and report this a fracture rate per 1,000 years of observation per study. We pooled the data with a random effects meta-analysis calculating the incident rate ratio (IRR) to compare the rate of fracture between the two groups [33]. In accordance with the Cochrane reviewers handbook [33] heterogeneity was assessed with the I^2 statistic and scores of 25%, 50% and 75% were classed as low, medium and high heterogeneity accordingly. We assessed publication bias with the visual inspection of a funnel plot [33] and the begg [34] and egger [35] tests. Due to the anticipated dearth of studies and the heightened risk of obtaining a spurious result, we did not conduct moderator analysis with our results [33]. All analysis was conducted with Statsdirect and is presented with 95% confidence intervals (CI).

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Results

Search results and study selection

The initial search identified 423 publications. After removal of duplicates, 367 abstracts and titles were screened (Figure 1). At the full text review stage, 44 articles were considered and 36 were subsequently excluded with reasons, leaving 8 articles that were included in the review. Details regarding the search results including reasons for exclusion of articles are summarised in figure 1.

Figure 1 here

Study and participant characteristics

Among the 8 included studies, 6 investigated the number of fractures among people with schizophrenia and a control group [36-41] including 48,384 people with schizophrenia and 3,945,783 people without mental illness. A further 2 studies reported the number of people with schizophrenia in a group of people with and without fractures (n=549 schizophrenia; [42,43]). Of the included studies only 4 set out with the primary objective to investigate the relationship between schizophrenia and fractures [36-38,42]. The summary of the groups of studies are presented in table 1 and 2 respectively. The average age among the participants ranged from 49.9 years [36] to 75.2 years [38]. The fracture sites considered varied in each study but the hip was the most commonly investigated [36-38,42,43]. None of the included studies contained clear information on the possible causes of fractures such as falls or accidents. Information regarding antipsychotic medication and other risk factors for osteoporosis and fractures was sparse among the included studies.

Table 1 and 2 here

Methodological quality

The NOS summary score for each article is presented in tables 1 and 2. All of the articles were of acceptable methodological quality with an average NOS score 6.25 (range 5-8).

Narrative results

Studies comparing the rate of fractures in people with schizophrenia and a control group

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In a study among female patients with schizophrenia, Bishop et al [40] established that those with schizophrenia (13%) were more likely to have experienced a fracture in the past 12 months than the control group (0%, p<0.001). More recently, Kelly et al [41] investigated fractures over the past 12 months among 1,898 females with psychosis and 14,985 controls without any history of mental illness or substance use disorder. The authors [41] established that similar proportions of people with psychosis (0.2%) and the control group had a fracture recorded in their medical records (0.3% control group). Jung et al [39] investigated the number of any fracture confirmed from radiograph among 229 inpatients with schizophrenia and established a higher rate among female patients (N=24, 25.8%) compared to the healthy controls of similar age (6.7%). The same results were evident among the male schizophrenia patients (N=31, 22.8%) compared to healthy male controls (4.6%).

Sorensen et al [36] conducted a national data linkage in Danish hospital registers investigating hip fractures including 15,431 patients with schizophrenia and 3,807,597 general population controls. The authors pooled data from 3,353,771 individuals and found that after adjusting for numerous established risk factors for fracture (sex, age, education, early retirement pension, physical comorbidity, lifetime corticosteroids, lifetime alcohol-related diagnosis, antidepressants, anticholinergics, and benzodiazepines) that a diagnosis with schizophrenia was associated with an increased risk for hip fracture (IRR=1.19, 95%CI=1.08–1.31). However, this effect was non-significant after the adjustment of antipsychotic medication (IRR=1.00, 95%CI=0.90–1.11). Sorensen et al [36] also investigated the impact of several medication classes consumed in the preceding 4 months on hip fracture and found in the unadjusted analysis that exposure to anticholinergics, antidepressants, benzodiazepines, antipsychotics (both low-potency, medium potency and high potency), olanzapine and quetiapine were all associated with a significantly increased risk of hip fracture. More specifically, when the authors compared the number of antipsychotic medications in the previous 4 months with those that had not taken any antipsychotic medication they found a dose response relationship of increased risk of hip fracture (IRR 1 antipsychotic=1.30 (95%CI=1.10–1.54), 2 antipsychotics 1.68 (95%CI=1.35–2.07) and> 2 antipsychotics 1.81 (95%CI=1.28–2.54). The authors

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also demonstrated there was a dose response relationship of increased risk of hip fracture among those on long term prolactin (IRR=1.16, 95%CI=1.09–1.24) and non-prolactin raising antipsychotic medication (IRR=1.23, 95%CI=1.15–1.32).

In a large nationwide study, Tsai et al [37] investigated the number of major fractures among 30,335 people with schizophrenia and 121,340 age and gender matched controls across a ten year period. The authors established that 5.5% of patients with schizophrenia had a major fracture compared to 3.5% in the control group ($p<0.001$). The authors [37] established that patients with schizophrenia with higher psychiatric proportion of days covered (PDC= total number of medication covered days divided by the number of days in a certain time period) established that there was no dose response relationship, with an increasing PDC not indicating a higher fracture risk implying that the frequency of psychiatric medicine dose did not have an effect on major fracture risk. However, the authors were not able to disentangle the influence of specific groups of psychotropic medication on fracture risk. Across the 10 year study[37] period 473 people with schizophrenia (from 1673) died following a major fracture compared to 784 (from 4257) in the control group. The calculation of the RR from the raw data established that people with schizophrenia were at a 54% increased risk of mortality after a major fracture compared to the control group (RR=1. 54, 95%CI=1.39 - 1.70). Lai et al [38] investigated hip fractures among a random sample of 445 patients with schizophrenia and 1,780 controls from the same cohort as Tsai et al [37]. The authors found that people with schizophrenia were significantly more likely to experience hip fractures (IRR 1.91, 95% CI 1.49, 2.44).

Rate of fractures per 1000 person years

There was sufficient raw data from 5 studies to calculate the rate of fractures per 1000 person years [37-41]. The rate of fractures per 1000 years were higher among participants with schizophrenia in 4 studies [37-40] whilst they were slightly lower in Kelly et al [41]. Full details are presented in table 3. It was possible to pool the adjusted rate of fractures from 5 studies [37-41] in each group. This established that the rate of fractures was 5.54 (95% CI 4.92 to 5.57) fractures per 1000 person years

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in those with schizophrenia and 3.48 (95% CI 3.39 to 3.64) fractures per 1000 person years in the control participants.

Table 3 here

Studies comparing the prevalence of schizophrenia in a fracture group and non-fracture group

Bolton et al [43] investigated hip, wrist and vertebral fractures from hospital records in Canada. The authors established that a diagnosis of schizophrenia is associated with fractures (OR=2.17, 95% CI 1.75-2.69). Howard et al [42] investigated 16,341 hip fracture cases in a UK general database study against 29,889 non-hip fracture cases. The authors established that people with a diagnosis of schizophrenia were more likely to experience a hip fracture (OR=1.37, 95% CI 1.32-2.28). However, in the adjusted analysis when the authors investigated the influence of gender they found that male and female patients were not at increased risk of experiencing hip fractures (see table 3).

Meta-analysis

It was possible to pool data from five studies [37-41] involving 32,593 unique participants with schizophrenia and 138,186 control participants. This established an IRR of 1.72 (95% CI = 1.24 to 2.39, I^2=49%; n= 168,914) and is displayed in figure 2a. The funnel plot for the main analysis was broadly symmetrical (figure 2b) and the Begg-Mazumdar (Kendall's tau = 0.33 P = 0.46) and Egger bias tests (= 0.49 P = 0.44) did not indicate any publication bias. In a subgroup analysis, we removed one study [41] with very low fracture rates in both groups and found an IRR of = 1.82 (95% CI = 1.33 to 2.50, I^2=47%, n schizophrenia=31,055, n controls=123,291).

Insert figure 2 and 2b here

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Discussion

General findings

To our knowledge this is the first systematic review and meta-analysis to investigate fractures in people with schizophrenia. Across the 8 eligible studies the results are unequivocal indicating that people with schizophrenia are at increased risk of fractures. Both the results from the narrative review and meta-analyses suggest that the increased risk of fracture is approximately 50-100% in people with schizophrenia compared to people without mental illness. Clearly this is of concern, especially in light of the increased mortality rate among people with schizophrenia following major fractures [37] which may be attributed to the longer hospital stays and increased adverse events that people with schizophrenia experience following fractures [26].

The reasons for the increased risk of fractures observed in people with schizophrenia are likely to be complex and multifactorial. However, heightened levels of osteoporosis and reduced bone mass seen in this population [7] are key factors since osteoporosis is a primary risk factor for fractures [44,45]. Only one study [39] reported osteoporosis in both groups and they established a considerable increased risk in the patient group (34.9% v 18.4%). The results from the narrative review also implicate antipsychotic medication as being a key factor, which is not surprising given a previous meta-analysis has demonstrated an increased risk for older adults in receipt of antipsychotics [8]. In their large national database study, Sorensen et al [36] demonstrated a clear dose response relationship between the number of antipsychotics and fracture risk in the 4 months immediately prior to fracture. Interestingly, although antipsychotic hyperprolactinaemia has been proposed as one mechanism reducing bone mineral density and increasing fracture risk [3,5,46], Sorensen et al [36] established there was a comparable increased risk of fractures for those taking prolactin raising and sparing medication. However, it should be noted the effects of antipsychotics induced hyperprolactinaemia influence on bone mineral density will accumulate over many years [5,47] and due to the age of participants it is likely that many participants in both groups may have taken 1st

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generation antipsychotics in the past for several years and so bone mineral density may have already been influenced in those taking prolactin sparing medication. Other known risk factors for falls and fractures such as the presence of depression, polypharmacy, hypertension, diabetes and pain [13] are all highly prevalent among people with schizophrenia yet, although sporadically reported in the current literature [37] there was insufficient data to clarify the importance of these factors on actual fractures.

Of the modifiable risk factors, lower limb muscle strength and balance are key predictors for falls and fractures in the general literature [13] and these are known to be impaired in people with schizophrenia [48,49]. Exercise is the most effective single intervention to prevent falls [50] and targeted exercise can improve lower limb strength, balance and may be integral in preventing falls and fractures in this patient group. When one considers that exercise is associated with a reduction in depressive symptoms and improved metabolic outcomes in people with schizophrenia [51] and that exercise may be equally effective as pharmacological interventions to prevent cardiovascular disease related mortality [52], then the central role of exercise in the treatment of schizophrenia is increasing. Research in the general medical literature [53] has demonstrated that better cardiorespiratory fitness is associated with shorter hospital stay and reduced mortality following major surgery. Recent research [54] has demonstrated that people with schizophrenia have greatly reduced cardiorespiratory fitness and exercise interventions should seek to improve this. To this end, physiotherapists and other specialists such as exercise physiologists may have particularly pertinent roles in the MDT management of schizophrenia [55]. However, clearly future research is required to investigate and clarify this rationale. Interestingly, Bishop et al [40] established that people with schizophrenia were less likely than the control group to receive osteoporosis screening and pharmacological interventions. This is in line with a deficit in general preventative medical care seen in this group [56,57].

Limitations

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Despite the fact this is the first review of its kind, it is important to consider a number of limitations which are predominantly reflected by limitations in the primary data. First, due to the paucity of data and lack of information it was not possible to conduct moderator or subgroup analyses with the results. Specifically, we could not clearly investigate the influence of increasing age, different medication classes, duration of antipsychotic exposure and other important risk factors for fractures on the pooled results. However, this is partially appeased by the narrative results which included several very large age and sex matched studies adjusting for several confounders and still found an increased risk. Second, most of the studies were cross-sectional or retrospective cohort studies. Future prospective studies are required to further understand fractures in people with schizophrenia. Third, there was heterogeneity in the reporting of fractures and in the skeletal sites considered thus precluding evaluation of site-specific fracture risk across the studies.

Future research

There are many research questions of relevance to the clinical care of people with schizophrenia that need addressing as a priority. First, there is a need to better understand the reasons why people with schizophrenia are more likely to experience fractures and in particular investigate the contributing mechanisms, with a view to developing prevention plans. Also, research investigating the care of people with schizophrenia in general hospitals following fracture is warranted to investigate: (a) how they can be rehabilitated in the best manner and avoid prolonged stays in hospital and (b) why they appear more susceptible to adverse events in the hospital but also are at increased risk of mortality thereafter [37]

In most of the studies we reviewed, the outcome was a fracture in any part of the skeleton and the circumstances in which the fracture incurred were not reported. Clearly, there is an urgent need to understand this in greater detail in order to prevent fractures in this group. There is a need for future prospective studies with specific outcome definitions, based on the site and the circumstances around the fracture to elucidate the potential mechanisms for the increased fracture

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risk observed in people with schizophrenia. It is highly likely that heightened levels of osteoporosis and osteopenia reported in people with schizophrenia [7] increase the risk for fractures. Investigations of mobility limitations and falls risk in people with schizophrenia should be considered since deficits in these areas are primary causes of falls and fractures in the general population [44,45]. Future research could also consider the prospective investigation of falls to see if this is increased in people with schizophrenia compared to the general population.

Finally, our results show the importance of including fracture outcomes in prospective studies that provide individual patient level data in order to establish the attributable risk of schizophrenia on fracture, as well as the contribution of specific risk factors, including age, gender, race, weight, smoking, physical activity behavior (e.g. complying with health recommendations or not) and psychotropic medication use (e.g. use of long term prolactin raising medication or not, the use of benzodiazepines or not, etc.). Next to this, validation of fracture prediction algorithms used in the general population, such as FRAX [58] for people with schizophrenia might be an important area of future research to identify those most at risk of fracture.

Conclusion

Our systematic review and meta-analysis has demonstrated that people with schizophrenia are at increased risk of developing fractures. The exact reasons for this are not yet clear but antipsychotic medications are likely to contribute. Limitations in the primary data did not enable us to elucidate the underlying contributors and causes of fractures and there is a need for future prospective research to better understand this. In addition, in light of the concerns regarding increased morbidity and mortality among people with schizophrenia experiencing a fracture, there is a need to develop preventative interventions to stop fractures occurring and this should include the wider multidisciplinary team.

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Conflict of Interest

BS, FG, AJM, RF, AS, SR have no conflict of interest related to this work.

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Figure 1. PRISMA 2009 flow diagram for search strategy

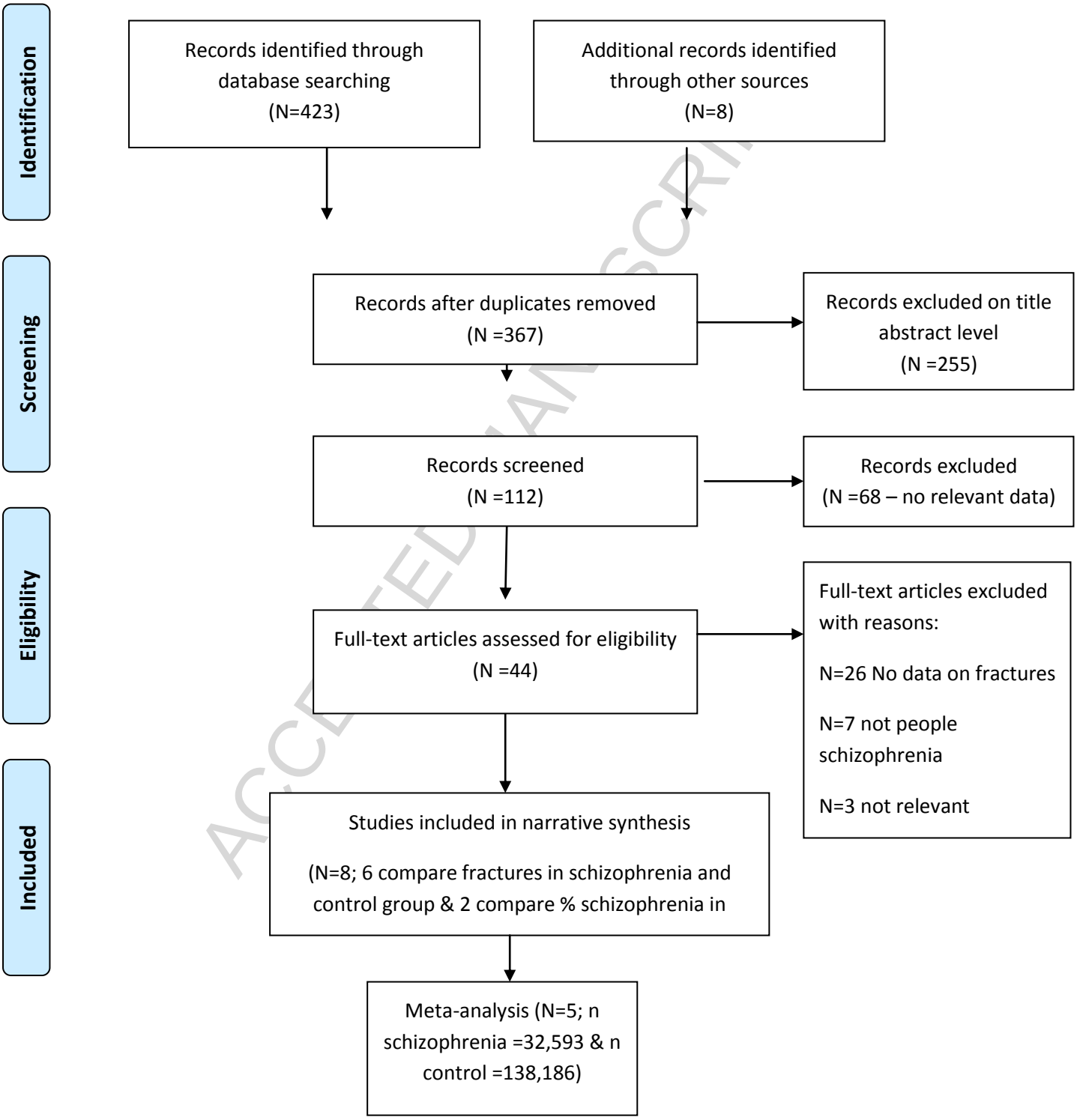

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Figure 2a Forest plot for the main meta-analysis

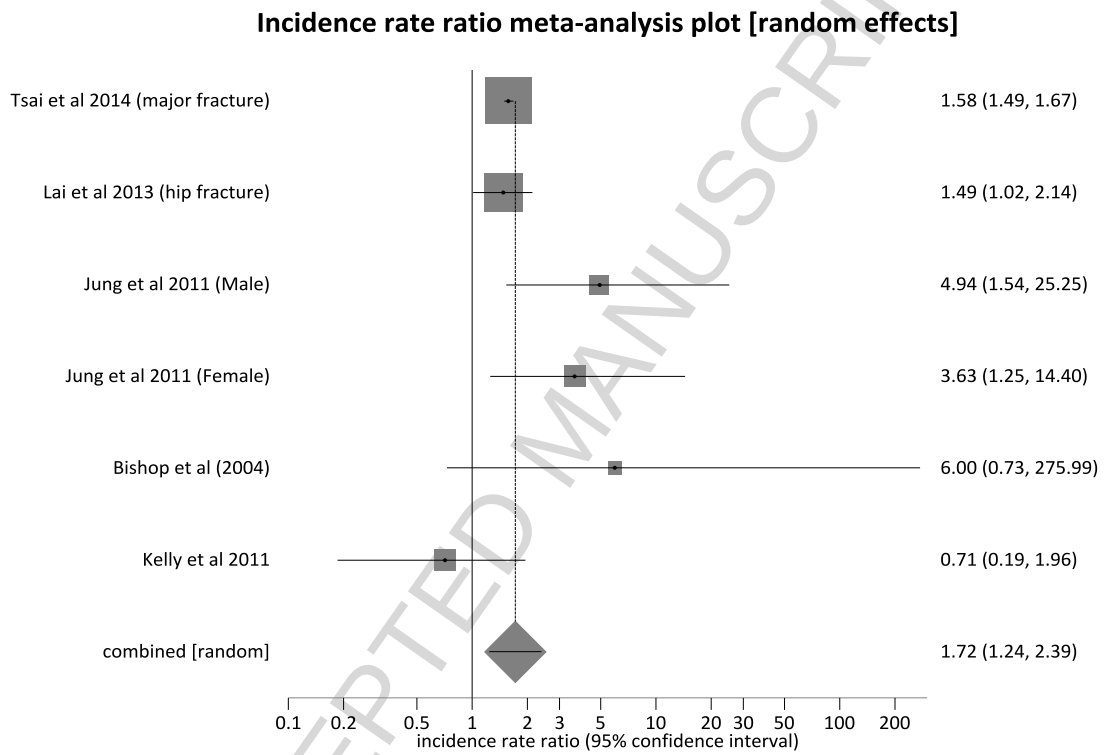

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Figure 2b funnel plot for the main analysis

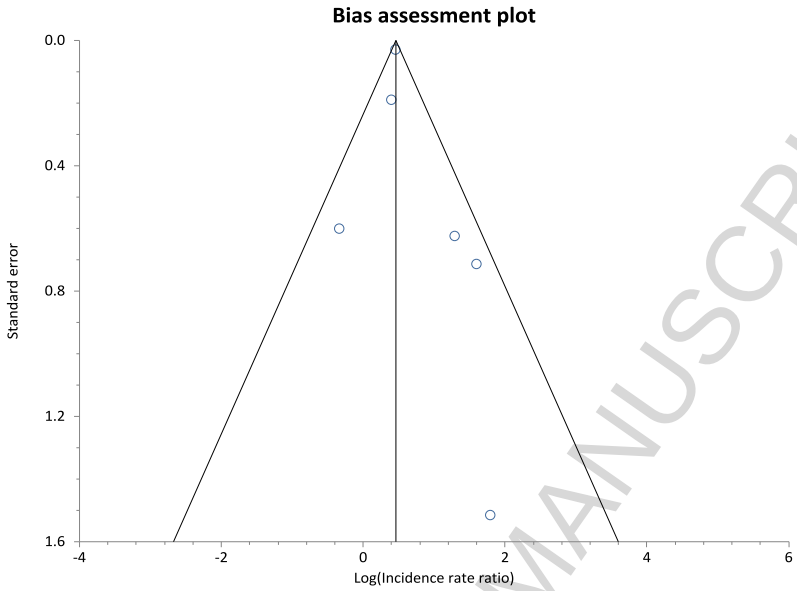

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Table 1 – summary of included studies comparing the prevalence of fractures among people with schizophrenia compared to a control group

Study	Location and design	Schizophrenia Diagnosis	Schizophrenia Participants	Control participants	Fracture site and ascertainment	NOS score
Bishop et al 2004	US, retrospective study	DSMI IV	N=46 100% female 61.1 years	N=46 100% female 61.0 years	Fracture in past 12 months Medical records	5
Kelly et al 2011	US, retrospective cohort	ICD 9	N=1898 schizophrenia (psychosis) 100% female 56 years	N=14,985 healthy controls free from mental illness and substance use disorder 100% female 57 years	Any fracture in past 12 months Medical records	6
Jung et al 2011	Republic of Korea, cross sectional	DSM IV	N=229 inpatients 40.6% female Mean duration illness 142.6±79.2 months N=93 female, 59.1 years 91.4% FGA % 8.6% SGA N=136 male, 58.2 years 121 (89.0%) FGA and SGA 15 (11.0%) 34.9% osteoporosis	N=125 healthy controls 48% female N=60 female, 58.2 years N=65 males, 59.0 years 18.4% osteoporosis ($p<0.01$)	Any fracture across lifetime Medical records	7
Sorensen et al 2013	Denmark, Cohort study	ICD 8 and ICD 10	N= 15,431 41% female 49.9 years	N= 3,807,597 56.9% female 46.9 years	Hip fracture Medical records	8
Lai et al	Taiwan, cross	ICD 9	N=445	N= 1780	Hip fracture	5

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2013	sectional		52.8% female 75.2 years	52.8% female 74.2 years	Medical records	
Tsai et al 2014	Taiwan, prospective cohort	ICD 9	N= 30,335 51.13% female 51.11 years	N= 121,340 51.13% female 51.11 years Age and gender matched no mental illness	Major fracture (vertebra, hip, humerus, forearm, wrist) Medical records	8

Key = FGA=first generation antipsychotic medication, SGA = second generation antipsychotic medication

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Table 2 – Summary of included studies investigating the prevalence of schizophrenia in comparative studies of those with and without a fracture

Study	Location and design	Schizophrenia Diagnosis	Schizophrenia Participants with fracture	Schizophrenia participants without fracture	Fracture site and ascertainment	NOS score
Howard et al 2007	UK, retrospective cohort	GP records ICD 9	N=100 hip fracture cases with schizophrenia (0.61% of all cases)	N=110 people with schizophrenia non-hip fracture cases (0.37% of all non-fracture cases)	Hip fracture Medical records	6
Bolton et al 2008	Canada, retrospective cohort	ICD 9	N= 142 fracture cases with schizophrenia (0.9% of all fracture cases) No demographic data All> 50 years	N=197 people with schizophrenia did not have a fracture (0.4% of all non-fracture cases) All > 50 years	Hip, wrist vertebral Medical records	5

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Table 3 – Results of included studies

Study	Type of fracture	Results
Sorensen et al 2013	Hip fracture	Diagnosis of schizophrenia IRR 1.19 (95% CI 1.08–1.31) [a] Diagnosis of schizophrenia & adjusted for AP IRR 1.00 (95% CI 0.90–1.11) [a] **Medications taken in past 4 months prior to hip fracture** Anticholinergics IRR 1.46 (95% CI 1.26–1.70) [b] Antidepressants IRR 1.29 (95% CI 1.09–1.54) [b] Benzodiazepines IRR 1.34 (95% CI 1.14–1.58) [b] Antipsychotics IRR 1.42 (95% CI 1.21–1.65) [b] Number of antipsychotics taken: 1 IRR 1.30 (95% CI 1.10–1.54) [b] 2 IRR 1.68 (95% CI 1.35–2.07) [b] >2 IRR 1.81 (95% 1.28–2.54) [b] Long term prolactin raising antipsychotic medication (IRR 1.16 95% CI 1.09–1.24) Long term non prolactin raising antipsychotic medication (IRR 1.23 95% CI 1.15–1.32).
Bishop et al 2004	Fracture in past 12 months	Schizophrenia participants 130.43 (95% CI 47.86-283.90) fractures per 1000 person years Control participants 21.73 (95% CI 0.55-121.122) fractures per 1000 person years. IRR 6.00 (95% 0.72-275.98) calculated from raw data
Howard et al 2007	Hip fracture	Diagnosis of schizophrenia OR 1.37 (95% CI 1.32-2.28) unadjusted univariate Adjusted analysis: Female diagnosis with schizophrenia OR 1.01 (95% CI 0.72-1.40) Male diagnosis with schizophrenia OR 1.61 (95% CI 0.81-3.19)
Bolton et al 2008	Hip, wrist, vertebral	Diagnosis schizophrenia OR 2.17 (95% CI 1.75-2.69)
Jung et al 2011	Lifetime	Male participants with schizophrenia 3.86 (95% CI 2.62-5.48) fractures per 1000 person

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	fracture	years. Female participants with schizophrenia 4.10 (95% 2.62-6.10) fractures per 1000 person years Male control participants 0.782(95% CI 0.160-2.28) fractures per 1000 person years. Female control participants 1.12 (95% 0.30-2.89) fractures per 1000 person years. IRR 4.93 (95% 1.54-5.24) male participants IRR 3.63 (95% CI 1.24-14.40) female participants Calculated from raw data.
Kelly et al 2011	Fracture in past 12 months	Schizophrenia participants 2.10(95% CI 0.57-5.39) fractures per 1000 person years. Control participants 2.95 (95% 2.14 3.96) fractures per 1000 person years IRR calculated from raw data 0.71 (95% 0.18- 1.95)
Lai et al 2013	Hip fracture	Schizophrenia participants 9.43 (95% CI 6.80-12.75) fractures per 1000 person years. Control participants 6.34 (95% CI 5.23-7.63) fractures per 1000 person years IRR for hip fracture among people with schizophrenia v control group IRR 1.91 (95% CI 1.49, 2.44) IRR calculated from raw data 1.49 (95% CI 1.01-2.03)
Tsai et al 2014	Major fracture Hip fracture	Schizophrenia participants 5.52 (95% CI 5.26-5.79) major fractures per 1000 person years. Control participants 3.50 (95% CI 3.40-3.61) major fractures per 1000 person years Schizophrenia participants 2.66 (95% CI 2.47-2.85) hip fractures per 1000 person years. Control participants 1.02 (95% CI 0.96-1.07) hip fractures per 1000 years. IRR major fracture 1.57 (95% CI 1.48-1.66) from raw data IRR hip fracture 2.60 (95% CI 2.38-2.85) from raw data

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		Hazard ratio [c] for osteoporotic fracture investigating psychiatric proportion of days covered (PDC) an indicator of the intensity of drug exposure in patients with schizophrenia PDC = 0 HR 1.192 (95% CI 0.946–1.502) 0 PDC ≦ 0.1 HR 1.190 (95% CI 0.968–1.464) 0.1PDC ≦ 0.2 HR 1.373 (95% CI 1.059–1.782) 0.2 PDC ≦ 0.3 HR 1.829 (95% CI 1.448–2.310) 0.3 PDC ≦ 0.4 HR 1.829 (95% CI 1.448–2.310) 0.4 PDC ≦ 0.5 HR 1.352 (95% CI 1.074–1.702) 0.5 PDC ≦ 0.6 HR 1.695 (95% CI 1.388–2.071) 0.6 PDC ≦ 0.7 HR 1.898 (95% CI 1.591–2.265) 0.7 PDC ≦ 0.8 HR 1.563 (95% CI 1.298–1.883) 0.8 PDC ≦ 0.9 HR 1.500 (95% CI 1.255–1.792) 0.9 b PDC ≦ 1 HR 1.840 (95% CI 1.649–2.053)

Key [a] (Sorensen et al 2013) adjusted for sex, age, education, early retirement pension, CPDS, lifetime corticosteroids, lifetime alcohol-related diagnosis, antidepressants, anticholinergics, and benzodiazepines [b] (Sorensen et al 2013) Adjusted for sex, age at diagnosis, alcohol misuse and somatic score. [c] (Tsai et al 2014) adjusted for age, gender, osteoporotic fracture-related illnesses, level of urbanization, and socioeconomic status

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