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Schizophrenia and the risk of fractures

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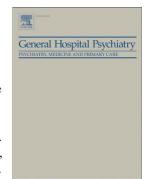
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Schizophrenia and the risk of fractures: A systematic review and comparative meta-analysis

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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, I²=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

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

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

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

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.

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 10³¹) 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

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

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 12 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).

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

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

also demonstrated there was a dose response relationship of increased risk of hip fracture among those on long term prolactin (IRR=1.16, 95%Cl=1.09–1.24) and non-prolactin raising antipsychotic medication (IRR=1.23, 95%Cl=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 study³⁷ 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

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

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 However, it should be noted the effects of antipsychotics induced sparing medication. 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

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

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

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.

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

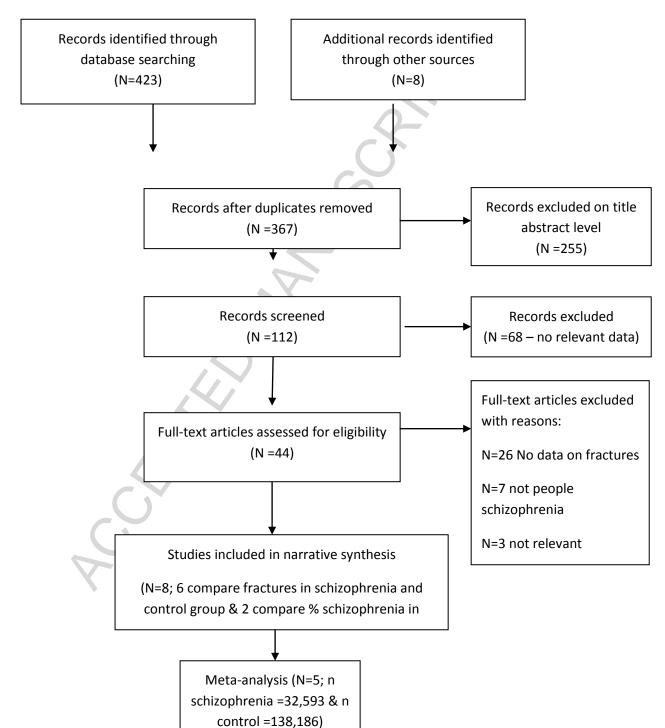


Figure 2a Forest plot for the main meta-analysis

Incidence rate ratio meta-analysis plot [random effects]

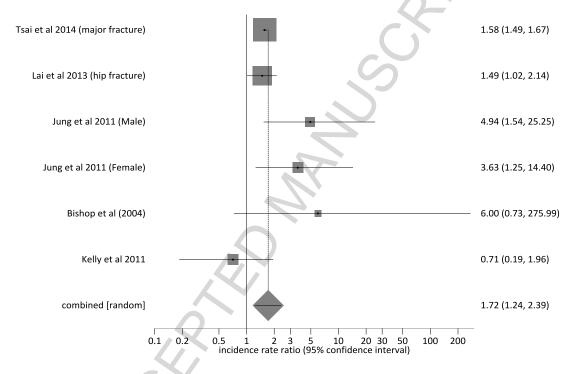


Figure 2b funnel plot for the main analysis

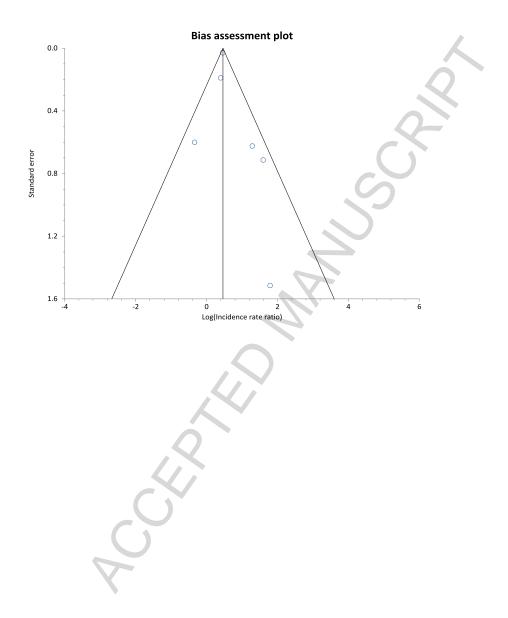


Table 1 – summary of included studies comparing the prevalence of fractures among people with schizophrenia compared to a control group

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

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

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

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

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

Table 3 – Results of included studies

Study	Type of fracture	Results
Sorensen et al Hip fracture		Diagnosis of schizophrenia IRR 1.19 (95% CI 1.08–1.31) a
2013		
		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 <u>IRR 1.34 (95% CI 1.14–1.58)</u> 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	Fracture in past	Schizophrenia participants 130.43 (95% CI 47.86-283.90) fractures per 1000 person years
2004	12 months	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	Hip fracture	Diagnosis of schizophrenia
2007		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	Hip, wrist,	Diagnosis schizophrenia
2008	vertebral	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

	fun atuus	1,120,12
	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 <u>4.93 (95% 1.54-5.24)</u> male participants
		IRR 3.63 (95% CI 1.24-14.40) female participants
		Calculated from raw data.
Kelly et al 2011	Fracture in pact	Schizophrenia participants 2.10(95% CI 0.57-5.39) fractures per 1000 person years.
Kelly et al 2011	Fracture in past	
	12 months	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)
		4/7
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)
		<u> </u>
Tsai et al 2014	Major fracture	Schizophrenia participants 5.52 (95% CI 5.26-5.79) major fractures per 1000 person years.
1301 Ct 01 2014	iviajoi iractare	Control participants 3.50 (95% CI 3.40-3.61) major fractures per 1000 person years
	Llin fracture	Control participants 3.30 (33% Ci 3.40-3.01) major fractures per 1000 person years
	Hip fracture	Cabinanh ranja participants 2 CC (050/ CL2 47 2 05) him fractures non 1000 paragrays
		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
	1	

Ha	azard ratio ^c for	osteoporotic fracture investigating psychiatric proportion of days covered
(P	DC) an indicato	r of the intensity of drug exposure in patients with schizophrenia
PC	OC = 0	HR 1.192 (95% CI 0.946–1.502)
10	PDC ≦ 0.1	HR 1.190 (95% CI 0.968–1.464)
0.3	1PDC ≦ 0.2	HR 1.373 (95% CI 1.059–1.782)
0.3	$2 \text{ PDC} \leq 0.3$	HR 1.829 (95% CI 1.448–2.310)
0.3	$3 \text{ PDC} \leq 0.4$	HR 1.829 (95% CI 1.448–2.310)
0.4	4 PDC ≦ 0.5	HR 1.352 (95% CI 1.074–1.702)
1.0	5 PDC ≦ 0.6	HR 1.695 (95% CI 1.388–2.071)
0.6	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	8 PDC ≦ 0.9	HR 1.500 (95% CI 1.255–1.792)
0.9	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