General Hospital Psychiatry 37 (2015) 126–133

Contents lists available at ScienceDirect

General Hospital Psychiatry

journal homepage: http://www.ghpjournal.com

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

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ARTICLE INFO

Article history:
Received 3 November 2014
Revised 9 January 2015
Accepted 9 January 2015

Keywords:
Schizophrenia
Psychosis
Fracture
Osteoporosis
Fragility fracture

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 until October 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 were narratively synthesized, 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% confidence interval (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 an increased rate of fractures compared to control participants (IRR 1.72, 95% CI=1.24–2.39, I^2=49%; n=168,914). There were insufficient data to conduct moderation analysis, but the narrative review consistently highlighted that 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.

1. 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 that is associated with antipsychotic-induced hyperprolactinemia and osteoporosis [5] and falls [8,9], which are a leading cause of fracture due to trauma. Moreover, people with schizophrenia engage in lower

Conflicts of interest:
B.S., A.J.M., R.F., A.S. and S.R. have no conflict of interest related to this work.
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.
Dr Davy Vancampfort is funded by the Research Foundation-Flanders (FWO-Vlaanderen). Fiona Gaughran has received honoraria for advisory work and lectures from Roche, BMS, Lundbeck, and Sunovion and has a family member with professional links to Lilly and GSK.

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http://dx.doi.org/10.1016/j.genhosppsych.2015.01.004
0163-8343/

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 postoperative infection rates, worse ambulatory rates after 1 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 postfracture (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 [odds ratio (OR), 1.2; 95% confidence interval (CI)=1.2–1.3; $P<.001$).

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 health care 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.

2. 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.

2.1. Inclusion and exclusion criteria

We included observational studies (prospective, retrospective or cross-sectional) that (a) included people with a diagnosis of schizophrenia according to recognized criteria (*Diagnostic and Statistical Manual of Mental Disorders (DSM), Fifth Edition* [30] or *International Classification of Diseases (ICD), 10th Revision* [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 1-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.

2.2. 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.

2.3. 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.

2.4. Data extraction

Two authors independently extracted data in a predetermined database. The data collected from each article included study design, geographical location and 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).

2.5. 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 nonrandomized trials and has acceptable validity and reliability [32]. The assessment tool focuses on three main methodological features: (a) the selection of the groups, (b) the comparability of the groups and (c) the ascertainment of the outcome of interest. Studies were given a NOS score ranging from 0 to 9, with a score of 5 or greater indicative of satisfactory methodological quality.

2.6. 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 utilized 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 of fractures across studies of differing time points and report this a fracture rate per 1000 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