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Study protocol for the systematic review and meta-analyses of the association between schizophrenia and bone fragility

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ABSTRACT

Introduction Individuals with schizophrenia are known to be at higher risk of comorbid conditions, both physical and psychological. Osteoporosis is possibly one of these, leading to public health concerns due to higher rates of associated mortality and morbidity. We aim to systematically search all available evidence across electronic databases regarding the relationship between schizophrenia and bone fragility.

Methods and analysis A systematic search of the research databases CINAHL, MEDLINE Complete, Embase and PsycINFO will be conducted and identified papers reviewed for eligibility, with a second reviewer confirming inclusions. Searches will be run from database inception to 1 October 2020 and supplemented by the hand checking of references of identified articles. A previously published scoring system will be used for assessing the methodological quality and risk of bias. A meta-analysis is planned.

Ethics and dissemination Due to including published literature only, ethical permission will not be necessary. Results of this study will be published in a relevant scientific journal and presented at a conference in the field of interest.

PROSPERO registration number CRD42020171959.

Strengths and limitations of this study

- We will apply comprehensive literature searches including index terms, entry terms and keywords.
- Two independent reviewers will extract the data and assess the methodological integrity of each study.
- Studies will not be excluded based on language or nationality of the studied populations.
- The planned meta-analysis is contingent on quantity, quality and/or heterogeneity of available evidence.
- There is a possibility that indigenous populations may not be captured.

INTRODUCTION

Schizophrenia is a severe and chronic relapsing disorder associated with marked functional impairment.[1] The lifetime prevalence of schizophrenia is approximately 1%, with the incidence nearing 1.5 per 10 000 people.[2] In Australia, the number of patients experiencing psychosis and receiving treatment in a period of 1 month is about 4.7 per 1000.[3] This disease is prevalent in both males and females, although symptoms generally develop earlier in men.[4] Schizophrenia has been attributed to an increased risk of a number of health conditions across various systems, including metabolic syndrome, cardiovascular disease, diabetes,[5 6] obstetric complications and cognitive impairments compared with the general population.[7 8] Osteoporosis, or bone fragility, is another condition that has more recently come under the spotlight.

Osteoporosis is 'a systemic skeletal disease characterised by low bone density and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture'.[9] Due to the higher rates of mortality, morbidity and disability stemming from osteoporosis, it is of significant public health concern.[10 11] In 2011, it was estimated that more than 1.2 million Australians had osteoporosis,[12] with this expected to reach 6.2 million by 2022.[13] Tatangelo *et al* reported the direct annual cost of osteoporosis, osteopenia (low bone mass) and fracture for those aged 50 or older was $A3.44 billion.[14]

Approximately 20 years ago, the high incidence of osteoporosis and osteoporotic fractures in patients with schizophrenia was first noted.[15 16] Since then, several studies have shown that compared with the general population, people living with schizophrenia have low Bone Mineral Density (BMD) and are at increased risk of fracture and osteoporosis.[17–20] A meta-analysis of the prevalence of low bone mass in individuals with schizophrenia reported that approximately one in eight patients with schizophrenia had osteoporosis, and this disease is over two and a half times more common in people with

schizophrenia than controls.[21] In a systematic review of clinical studies comparing BMD in individuals with schizophrenia compared with controls found 15 out of the 16 studies included reported an increased prevalence of osteoporosis among those with schizophrenia.[20] Other bone endpoints in the context of schizophrenia including bone quality, bone loss over time and bone turnover are yet to be investigated systematically.

The cause of the observed deficits in BMD in these patients is complex and likely to be multifactorial.[21 22] Both the disease[23] and related lifestyle/medical factors[24] associated with schizophrenia itself are likely to all play a role (eg, smoking,[25 26] alcohol abuse,[22 27] sedentary lifestyle,[25] reduced exposure to sunlight,[28] vitamin D[29] and calcium deficiency, poor nutrition,[30 31] diabetes mellitus[32] and polydipsia.[33] Furthermore, antipsychotic drugs themselves are associated with an increased risk of osteoporosis and fracture, compounding this association.[34 35]

Objectives

This aim of this systematic review is to:

1. Identify studies investigating an association between schizophrenia and bone fragility (defined as BMD, bone loss, osteoporosis, fracture, bone quality and bone turnover).
2. Assess the quality of each included study.
3. Identify any potential confounding and/or mediating factors in the link between schizophrenia and bone fragility.

METHODS

Eligibility criteria

Cross-sectional, case–control and/or cohort studies investigating the association between schizophrenia (defined by medical records or diagnoses based on Diagnostic and Statistical Manual of Mental Disorders or International Classification of Disease criteria) and bone fragility (defined as BMD, bone loss, osteoporosis, fracture, bone quality and bone turnover) in samples of adults aged ≥18 years, of any nationality and published in any year or language are eligible for inclusion. Clinical trials, grey literature, case reports, theses and conference presentations are ineligible.

Search strategy

Studies will be identified via electronic searches of research databases in the area of medical, health and social sciences (CINAHL Complete, Embase, MEDLINE Complete and PsycINFO). Searches will be conducted up to 1 October 2020. The following index terms (CINAHL SH/Emtree/MeSH/APA Thesaurus PIT) will be searched: "schizophrenia" AND ("osteoporosis" OR "bone disease, metabolic" OR "fractures, bone" OR "bone and bones" OR "bone density" OR "absorptiometry, photon"). The entry terms of each MeSH will be searched as title and abstract (TI/AB). The entry terms for "absorptiometry, photon" are "Dual energy x-ray absorptiometry, DXA, DEXA, densitometry". The entry terms for "bone diseases, metabolic" are "osteopenia, bone loss". The entry terms for "bone density" are "bone mineral density, BMD". The following keywords will also be included: quantitative heel ultrasound, bone turnover markers, bone health, bone fragility and bone quality. Relevant truncation and wildcard symbols will be applied for each database if appropriate.

Data management and extraction

The online reference management database, Covidence,[36] will be used for data management. Citation screening and full-text review, finding and removing of duplicated references and extraction of study characteristics and outcomes will be undertaken in this programme. The search strategy will be undertaken by the first reviewer to identify eligible articles. The first reviewer will also handsearch reference lists of the included studies. A further reviewer will confirm the eligibility of the identified articles. Translators will be used if articles are identified in languages other than English.

Assessment of methodological quality

Methodological quality will be determined using the scoring system by Lievense *et al*.[37] Two reviewers will independently score included studies, with a third providing final judgement should any discrepancy in scores arise. A meta-analysis is planned, however, if not possible due to methodological heterogeneity, a 'best evidence synthesis will be undertaken.

Patient and public involvement

There was no patient involvement.

Presenting and reporting results

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocol guidelines[38] have been followed and the review will conform to PRISMA reporting guidelines.[39] The Quality of Reporting of Meta-analyses (QUOROM) diagram will be used to document numbers and reasons concerning included vs excluded studies in the context of the prespecified eligibility criteria.[40]

Factors playing a role in the association between schizophrenia and bone fragility will be identified. These factors may consist of related lifestyle/medical factors, such as smoking, alcohol abuse, sedentary lifestyle, vitamin D and calcium deficiency, poor nutrition, diabetes mellitus and polydipsia.

We intend to conduct a meta-analysis; nevertheless, a 'best evidence synthesis'[41] will be completed if a numeral synthesis is not achievable due to methodological heterogeneity. The level of evidence will be categorised using

four categories ranging from no evidence to strong evidence.

Ethics and Dissemination

Results will be presented in a related scientific journal and findings presented at scientific conference/s relevant to mental healthand bone.

Due to including published data only, ethical permission is not required. Nevertheless, ethical and governance standards will be abided by, in respect to data management, presentation and dissemination of results.

DISCUSSION

This systematic review will identify andevaluate the currently available evidence regarding the association between schizophrenia and bone fragility. Furthermore, this review will provide an up-to-date evidence base for which public health strategies aimed at reducing the burden associated with bone fragility associated with schizophrenia could be founded.

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Contributors BAM, JAP and LJW conceptualised the research question for this protocol. ALS, JMH, KC and MB revised and edited the research question. The search strategy was developed by BAM, JAP and LJW and reviewed by a librarian (BK). The methodological processes have been revised and approved by all authors (BAM, ALS, JAP, JMH, KC, MB and LJW). BAM and LJW drafted this manuscript. All authors (BAM, ALS, JAP, JMH, KC, MB and LJW) read, edited and approved the final version and guarantee the review.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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