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A 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 PsychINFO will be conducted and identified papers reviewed for eligibility, with a second reviewer confirming inclusions. 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.

Registration details: This systematic review has been registered with PROSPERO.

Keywords: MeSH terms: schizophrenia, osteoporosis, “bone disease, metabolic”, “fractures, bone”, “bone and bones”, “bone density”, “absorptiometry, photon”.

Other keywords: quantitative heel ultrasound, bone turnover markers, bone health, bone fragility and bone quality.

Strengths and limitations of this study

- This review will thoroughly examine the association between schizophrenia and bone fragility.
- Comprehensive literature searches including index terms, entry terms and keywords will be applied, and up-to-date systematic review methodologies will be used to identify the evidence of interest.
- 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 population.
- Quality assessment of included studies will be reported.

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 10000 people[2]. In Australia, the number of patients experiencing psychosis and receiving treatment in a period of one month is about 4.7 per 1000[3]. This disease is prevalent in both males and females, although symptoms generally develop earlier in men. Schizophrenia has been attributed to an increased risk of a number of health conditions across various systems, including metabolic syndrome, cardiovascular disease, diabetes[4,5], obstetric complications and cognitive impairments compared with the general population[6,7]. 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 micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture"[8]. Due to the higher rates of mortality, morbidity and disability stemming from osteoporosis, it is of significant public health concern[9,10]. In 2011, it was estimated that more than 1.2 million Australians had osteoporosis[11], with this expected to reach 6.2 million by 2022[12]. Tantangelo (2017) reported the direct annual cost of osteoporosis, osteopenia (low bone mass), and fracture for those aged 50 or older was AUD 3.44 billion[13].

Approximately 20 years ago the high incidence of osteoporosis and osteoporotic fractures in patients with schizophrenia was first noted[14,15]. Since then, several studies have shown that compared with the general population, people living with schizophrenia have low BMD and are at increased risk of fracture and osteoporosis[16,17,18,19]. 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[20]. In a systematic review of clinical

studies comparing BMD in individuals with schizophrenia compared to controls found 15 out of the 16 studies included reported an increased prevalence of osteoporosis among those with schizophrenia[19].

The cause of the observed deficits in BMD in these patients is complex and likely to be multifactorial[20,21]. Both the disease[22] and related lifestyle/medical factors[23] associated with schizophrenia itself are likely to all play a role (e.g. smoking[24,25], alcohol abuse[22,26], sedentary lifestyle[24], reduced exposure to sunlight[27], vitamin D[28] and calcium deficiency, poor nutrition[29,30], diabetes mellitus[31], and polydipsia[32]). Furthermore, antipsychotic drugs themselves are associated with an increased risk of osteoporosis and fracture, compounding this association[33,34].

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 self-report, medical records or diagnoses based on Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of disease (ICD) 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). The following index terms (MeSH/Emtree/CINAHL SH) 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. Details of the systematic search strategy are depicted in the online supplementary tables.

Data management and extraction

The online reference management database, Covidence[35], 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 program. The search strategy will be undertaken by the first reviewer to identify eligible articles. The first reviewer will also hand-search reference lists of the included studies. A further reviewer will confirm the eligibility of the identified articles. Assistance will be sought if articles included are in a language other than English.

Assessment of methodological quality

Methodological quality will be determined using the scoring system by Lievense et al (2001)[36]. 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.

Presenting and reporting results

Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) guidelines[37] have been followed and the review will conform to PRISMA reporting guidelines[38]. A QUOROM diagram will be used to document numbers and reasons concerning included vs. excluded studies in the context of the pre-specified eligibility criteria[39].

Dissemination

This systematic review has been submitted for registration with PROSPERO. Results will be presented in a related scientific journal and findings presented at scientific conference/s relevant to mental health and bone.

Ethics

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

CONCLUSION

This systematic review will identify and evaluate the currently available evidence regarding the association between schizophrenia and bone fragility. The outcomes of this study will contribute to available literature by comprehensively investigating all bone endpoints. 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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Contributions

The search strategy was developed by BAM, JAP and LJW and reviewed by a librarian. The methodological processes have been revised and approved by all authors. BAM and LJW drafted this manuscript. All authors read, edited and approved the final version.

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Competing interests

None of the authors has any relevant conflicts of interest related to the work under consideration for publication. JAP has received grants from the NHMRC, Amgen, Deakin University and the Beischer Foundation. MB has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, Medical Benefits Fund, National Health and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, Meat and Livestock Board, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker for Astra Zeneca, Lundbeck, Merck, Pfizer, and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Lundbeck Merck, Pfizer and Servier. LJW has received Grant/Research support from Eli Lilly, Pfizer, The University of Melbourne, Deakin University and the NHMRC.

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PROSPERO registration number: CRD42020171959

Keywords: schizophrenia, osteoporosis, osteopenia, fracture, bone density, bone fragility, bone quality, bone health

Strengths and limitations of this study

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- Comprehensive literature searches including index terms, entry terms and keywords will be applied, and up-to-date systematic review methodologies will be used to identify the evidence of interest.
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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 10000 people[2]. In Australia, the number of patients experiencing psychosis and receiving treatment in a period of one 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 micro-architectural 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]. Tantangelo (2017) reported the direct annual cost of osteoporosis, osteopenia (low bone mass), and fracture for those aged 50 or older was AUD 3.44 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 BMD and are at increased risk of fracture and osteoporosis[17,18,19,20]. 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 to controls found 15 out of the 16 studies included reported an increased prevalence of osteoporosis among those with schizophrenia[20].

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 (e.g. 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 (DSM) or International Classification of disease (ICD) 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 program. The search strategy will be undertaken by the first reviewer to identify eligible articles. The first reviewer will also hand-search reference lists of the included studies. A further reviewer will confirm the eligibility of the identified articles. Translators will be utilised 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 (2001)[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 Review and Meta-Analysis Protocol (PRISMA-P) guidelines[38] have been followed and the review will conform to PRISMA reporting guidelines[39]. A QUOROM diagram will be used to document numbers and reasons concerning included vs. excluded studies in the context of the pre-specified 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.

Dissemination

This systematic review has been registered with PROSPERO (CRD42020171959). Results will be presented in a related scientific journal and findings presented at scientific conference/s relevant to mental health and bone.

Ethics

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

This systematic review will identify and evaluate the currently available evidence regarding the association between schizophrenia and bone fragility. The outcomes of this study will contribute to available literature by comprehensively investigating all bone endpoints. 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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Contributions

BAM, JAP and LJW conceptualised the research question for this protocol. ALS, JH, 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 of the authors have any relevant conflicts of interest related to the work under consideration for publication.

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Supplement: Completed PRISMA-P Checklist

A study protocol for the systematic review and meta-analyses of the association between schizophrenia and bone fragility.

Behnaz Azimi Manavi, Amanda Stuart, Julie A. Pasco, Jason Hodge, Kayla Corney, Michael Berk & Lana J. Williams

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Location in text
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Pg. 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Pg. 2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Pg.1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Pg. 8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Pg. 8
Sponsor	5b	Provide name for the review funder and/or sponsor	Pg. 8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Pg.8
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Pg. 4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Pg. 5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Pg. 5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Pg. 6

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Pg. 6
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Pg. 6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Pg. 6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Pg. 6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Pg. 6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Pg. 6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Pg. 6-7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Pg. 7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Pg. 7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Pg. 7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Pg. 7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Pg. 7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Health services research, Mental health, Medical publishing and peer review, Epidemiology, Research methods
Keywords:	PUBLIC HEALTH, Schizophrenia & psychotic disorders < PSYCHIATRY, Bone diseases < ORTHOPAEDIC & TRAUMA SURGERY, EPIDEMIOLOGY

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

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Data are available upon request.

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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 PsychINFO will be conducted and identified papers reviewed for eligibility, with a second reviewer confirming inclusions. Searches will be run from database inception until 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

Keywords: schizophrenia, osteoporosis, osteopenia, fracture, bone density, bone fragility, bone quality, bone health, mental disorders, psychiatry, neuroscience

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 10000 people[2]. In Australia, the number of patients experiencing psychosis and receiving treatment in a period of one 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 micro-architectural 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]. Tantangelo (2017) reported the direct annual cost of osteoporosis, osteopenia (low bone mass), and fracture for those aged 50 or older was AUD 3.44 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 BMD and are at increased risk of fracture and osteoporosis[17,18,19,20]. 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 to 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 (e.g. 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 (DSM) or International Classification of disease (ICD) 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 program. The search strategy will be undertaken by the first reviewer to identify eligible articles. The first reviewer will also hand-search reference lists of the included studies. A further reviewer will confirm the eligibility of the identified articles. Translators will be utilised 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 (2001)[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 Review and Meta-Analysis Protocol (PRISMA-P) guidelines[38] have been followed and the review will conform to PRISMA reporting guidelines[39]. A QUOROM diagram will be used to document numbers and reasons concerning included vs. excluded studies in the context of the pre-specified 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

This systematic review has been registered with PROSPERO (CRD42020171959). Results will be presented in a related scientific journal and findings presented at scientific conference/s relevant to mental health and 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 and evaluate 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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Contributions

BAM, JAP and LJW conceptualised the research question for this protocol. ALS, JH, 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 of the authors have any relevant conflicts of interest related to the work under consideration for publication.

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Supplement: Completed PRISMA-P Checklist

A study protocol for the systematic review and meta-analyses of the association between schizophrenia and bone fragility.

Behnaz Azimi Manavi, Amanda Stuart, Julie A. Pasco, Jason Hodge, Kayla Corney, Michael Berk & Lana J. Williams

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Location in text
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Pg. 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Pg. 2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Pg.1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Pg. 8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Pg. 8
Sponsor	5b	Provide name for the review funder and/or sponsor	Pg. 8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Pg.8
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Pg. 4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Pg. 5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Pg. 5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Pg. 6

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Pg. 6
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Pg. 6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Pg. 6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Pg. 6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Pg. 6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Pg. 6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Pg. 6-7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Pg. 7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Pg. 7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Pg. 7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Pg. 7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Pg. 7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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