

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	A study protocol for the systematic review and meta-analyses of the association between schizophrenia and bone fragility
<b>AUTHORS</b>	Azimi Manavi, Behnaz; Stuart, Amanda; Pasco, Julie; Hodge, Jason; Corney, Kayla; Berk, Michael; Williams, Lana

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Rawiri Keenan University of Waikato, Aotearoa/New Zealand
<b>REVIEW RETURNED</b>	13-Aug-2020

<b>GENERAL COMMENTS</b>	<p>while guidance from RAZNCP(<a href="https://www.ranzcp.org/files/resources/college_statements/clinician/cpg/cpg_clinician_full_schizophrenia-pdf.aspx">https://www.ranzcp.org/files/resources/college_statements/clinician/cpg/cpg_clinician_full_schizophrenia-pdf.aspx</a>) doesn't explicitly mention osteoporosis it worth while therefore in exploring this more through a meta analysis like this. I do struggle however with there being no mention of the plight of Indigenous populations, while mention is made of poor nutrition and diabetes etc, there is nothing acknowledging the role of poverty and social deprivation within Indigenous populations that generally leaves them over represented in hospitalisation and early death data from schizoaffective disorders</p> <p>while the study is looking overall at osteoporosis and schizophrenia, one limitation in any data is likely to be that Indigenous populations are missing from studies looking at such an outcome because they die much younger overall and often miss out in basic care and so is in my opinion worth touching on or considering in any study looking at schizoaffective disorders and its outcomes (your objective 3 lists this).</p>
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<b>REVIEWER</b>	Natalie Thomas Monash University, Australia
<b>REVIEW RETURNED</b>	20-Aug-2020

<b>GENERAL COMMENTS</b>	<p>Straight forward, clearly defined protocol presented for the systematic review and meta-analysis of the association between schizophrenia and bone fragility.</p> <p>Minor comments:</p> <ul style="list-style-type: none"> <li>• Missing reference for following statement: 'This disease is prevalent in both males and females, although symptoms generally develop earlier in men'.</li> <li>• It is worth clarifying how this study will differ from the 2014 meta-analysis of prevalence estimates and moderators of low bone mass in people with schizophrenia, Stubbs B et al (ie. to update,</li> </ul>
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	investigate different mediators/moderators etc?)  • 'Assistance will be sought if articles included are in a language other than English'- does this mean a translator will be used?
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# VERSION 1 – AUTHOR RESPONSE

- Reviewer: 1

- Please state any competing interests or state 'None declared':

Amendments to the text read as follows:

"None of the authors have any relevant conflicts of interest related to the work under consideration for publication." (page 8)

- while guidance from RAZNCP

([https://www.ranzcp.org/files/resources/college\\_statements/clinician/cpg/cpg\\_clinician\\_full\\_schizophrenia-pdf.aspx](https://www.ranzcp.org/files/resources/college_statements/clinician/cpg/cpg_clinician_full_schizophrenia-pdf.aspx)) doesn't explicitly mention osteoporosis it worthwhile therefore in exploring this more through a meta-analysis like this. I do struggle however with there being no mention of the plight of Indigenous populations, while mention is made of poor nutrition and diabetes etc, there is nothing acknowledging the role of poverty and social deprivation within Indigenous populations that generally leaves them over represented in hospitalisation and early death data from schizoaffective disorders while the study is looking overall at osteoporosis and schizophrenia, one limitation in any data is likely to be that Indigenous populations are missing from studies looking at such an outcome because they die much younger overall and often miss out in basic care and so is in my opinion worth touching on or considering in any study looking at schizoaffective disorders and its outcomes (your objective 3 lists this).

Thank you for this insightful comment. We agree that this needs to and will be acknowledged in the full manuscript. However, a detailed analysis of this topic is beyond the scope of this review.

Reviewer: 2

- Please state any competing interests or state 'None declared':

Amendments to the text read as follows:

Competing interests

"None of the authors have any relevant conflicts of interest related to the work under consideration for publication." (page 8)

- Missing reference for following statement: 'This disease is prevalent in both males and females, although symptoms generally develop earlier in men'

A reference has now been added.

Amendments to the text read as follows:

"Schizophrenia is a severe and chronic relapsing disorder associated with marked functional impairment<sup>1</sup>. The lifetime prevalence of schizophrenia is approximately 1%, with the incidence nearing 1.5 per 10000 people<sup>2</sup>. In Australia, the number of patients experiencing psychosis and

receiving treatment in a period of one month is about 4.7 per 10003. This disease is prevalent in both males and females, although symptoms generally develop earlier in men4.” (page 4)

“Häfner H. Gender differences in schizophrenia. Psychoneuroendocrinology 2003; 28: 17-54” (page 9)

- It is worth clarifying how this study will differ from the 2014 meta-analysis of prevalence estimates and moderators of low bone mass in people with schizophrenia, Stubbs B et al (ie. to update, investigate different mediators/moderators etc?).

The study conducted by Stubbs et al. (2014) was an important addition to the field, which identified studies that investigated low bone mass as defined by T- or Z-scores using the following search terms only: (osteoporosis or osteopenia or osteo\* or bone mineral density or DXA or DEXA or bone) AND (schizophrenia or schizo\* or psychosis). The current study will provide an update but not limit bone fragility endpoints thus includes a greater number of bone related index terms. 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 following keywords will also be included: quantitative heel ultrasound, bone turnover markers, bone health, bone fragility and bone quality.” (see page 6)

- ‘Assistance will be sought if articles included are in a language other than English’- does this mean a translator will be used?

Translators will be utilised if articles are identified in languages other than English.

Amendments to the text read as follows:

“Translators will be utilised if articles are identified in languages other than English.” (page 6)

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Dr Rawiri Keenan University of Waikato, New Zealand
<b>REVIEW RETURNED</b>	23-Sep-2020
<b>GENERAL COMMENTS</b>	Thank you for your revision and reply to my previous comment in regards to the plight of indigenous people in this area. I do hope and look forward to the actual review that will address this in some way. I have been thinking if there is a way you could comment in the the strengths and limitations of this review protocol? but equally I wonder if in strengths and limitations the statement "This review will thoroughly examine the association between schizophrenia and bone fragility" is false, you will find any literature on the topic rather than examine it?

## VERSION 2 – AUTHOR RESPONSE

- Reviewer: 1

Comments to the Author

Thank you for your revision and reply to my previous comment in regards to the plight of indigenous

people in this area. I do hope and look forward to the actual review that will address this in some way. I have been thinking if there is a way you could comment in the the strengths and limitations of this review protocol? but equally I wonder if in strengths and limitations the statement "This review will thoroughly examine the association between schizophrenia and bone fragility" is false, you will find any literature on the topic rather than examine it?

We agree with both points raised and have now updated the "Strengths and Limitation" section accordingly.

Amendments to the text read as follows:

"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." (page 3)