BMJ Open

Bipolar Disorder and Bone Health: A systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013981
Article Type:	Protocol
Date Submitted by the Author:	23-Aug-2016
Complete List of Authors:	Chandrasekaran, Vinoomika; Deakin University - Geelong Waterfront Campus, School of Medicine (IMPACT SRC) Brennan, Sharon; Deakin University - Geelong Waterfront Campus, Department of Medicine Stuart, Amanda; Deakin University, Pasco, Julie; The University of Melbourne, Clinical and Biomedical Sciences: Barwon Health Berk, Michael; Deakin University, IMPACT SRC Hodge, Jason; Deakin University - Waurn Ponds Campus, Geelong Centre for Emerging Infectious Diseases (GCEID); Barwon Health, Geelong Centre for Emerging Infectious Diseases (GCEID) Williams, Lana; Deakin University,
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Mental health, Public health
Keywords:	Bipolar Disorder, Bone Health, EPIDEMIOLOGY

Bipolar Disorder and Bone Health: A systematic review protocol

Vinoomika Chandrasekaran[1](vchandra@barwonhealth.org.au)
Sharon L Brennan-Olsen[1,2,3] (sbrennan@unimelb.edu.au)
Amanda L Stuart[1] (amandh@barwonhealth.org.au)
Julie A Pasco[1,2] (juliep@barwonhealth.org.au)
Michael Berk[1,4,5,6,7] (mikebe AT barwonhealth.org.au)
Jason M Hodge[1,7] (jasonh@barwonhealth.org.au)
Lana J Williams[1] (lanaw@barwonhealth.org.au)

[1]*Deakin University, Geelong, Australia*
[2]*Australian Institute for Musculoskeletal Science (AIMSS), The University of Melbourne, St Albans, Australia*
[3]*Institute for Health and Ageing, Australian Catholic University, Melbourne, Australia*
[4]*Department of Psychiatry, University of Melbourne, Parkville, Australia*
[5]*Florey Institute of Neuroscience and Mental Health, Parkville, Australia*
[6]*Orygen the National Centre of Excellence in Youth Mental Health, Parkville, Australia*
[7]*Barwon Health University Hospital, Geelong, Australia*

Author for correspondence:
Dr Lana Williams
Deakin University
School of Medicine
IMPACT Strategic Research Centre
PO Box 281, Geelong 3220, Australia
Tel: +61 3 4215 3303 Fax +61 3 4215 3491
Email: lanaw@barwonhealth.org.au

Word count: Manuscript: 1980; Abstract: 231

Keywords: bipolar disorder, bone, osteoporosis, fracture, systematic review, meta-analysis

Abstract

Introduction:

Bipolar Disorder is a chronic, episodic illness, associated with significant personal, social and economic burden. It is estimated to affect approximately 2.4% of the population worldwide and is commonly associated with psychological and/or physiological comorbidities. Osteoporosis is one such comorbidity; a disease of bone that is asymptomatic until a fracture occurs. This systematic review attempts to capture, collate, assess and discuss the literature investigating the association between bipolar disorder and bone health.

Methods and analysis:

We aim to identify articles that investigate the association between bipolar disorder and bone health in adults by systematically searching the Medline, PubMed, OVID and CINAHL databases. Two independent reviewers will determine eligibility of studies according to pre-determined criteria, and methodological quality will be assessed using a previously published scoring system. A meta-analysis will be conducted, and statistical methods will be used to identify and control for heterogeneity, if possible. If accurate numerical syntheses are prevented due to statistical heterogeneity, a best evidence synthesis will be conducted to assess the level of evidence for associations between bipolar disorder and bone.

Ethics and dissemination:

Ethical permission will not be required for this systematic review since only published data will be used. This protocol will be registered with PROSPERO. Findings of the review will be published in a peer-reviewed scientific journal, and will be presented to clinical and population health audiences at national and international conferences.

Strengths and limitations of this study:

- This systematic review will explore a novel and covert clinical area.
- It will comprehensively assess existing literature that investigates associations between bipolar disorder and bone health. We aim to a) identify the studies that match our search criteria; b) assess the methodological quality of those studies; c) identify factors that have been identified as potential confounders and/or mediators of the association between bipolar disorder and bone; and d) synthesise the findings accordingly.
- Two authors will independently confirm study selection, and undertake data extraction and methodological assessment.
- This systematic review will collate the existing evidence-base, in order to provide a comprehensive synthesis of research in this area.
- The definition and diagnostic criteria of bipolar disorder has been clearly outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD).
- A potential limitation of this review may be the paucity of data available due to this being a nascent area of enquiry, and that there may be much heterogeneity in available studies.

INTRODUCTION

Bipolar disorder, a mental disorder characterised by biphasic fluctuations in mood, is a severe, chronic, episodic illness, which generally necessitates pharmacotherapy and/or psychotherapy. It is estimated to affect approximately 2.4% of the population [1] and has been ranked the sixth leading cause of disability in the world, amongst individuals aged 15-44 years [2]. The related direct and indirect costs associated with bipolar disorder are substantial [3, 4]. The burden of bipolar disorder is experienced on many levels – by the sufferer, their immediate family and friends and also by the healthcare system. Symptom burden and disease course is often worsened in the presence of psychological and/or physiological comorbidities.

Psychiatric disorders, including bipolar disorder, have been associated with early mortality, with approximately 60% of this excess mortality due to chronic physical illness [5]. A particularly common comorbidity of unipolar depression is osteoporosis [6, 7]. Yet it is normatively overlooked, due to being asymptomatic until fracture occurs. Osteoporosis is a global public health issue, estimated to affect nearly 49 million individuals in industrialised countries, with this on the rise as a consequence of the ageing population. [8, 9]. The rising global economic burden, related to the direct and indirect costs of medical care and rehabilitation of individuals with osteoporotic fractures is concerning [10, 11]. Both clinically diagnosed unipolar depression and depressive symptoms have been shown to be associated with deficits in bone mineral density (BMD), bone loss over time and increased fracture risk in both, men and women [7, 12, 13]. Furthermore, antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs) used in treatment of depression have also been shown to be noxious to bone [14]. Other psychotropic medication, namely antipsychotics and anticonvulsants have also been shown to have a deleterious effect on bone [15-17]. A recent research synthesis with meta-analyses concluded that depression should be considered a serious risk factor for osteoporosis, based on aggregated data showing BMD among individuals with depression to be up to 7.3% lower [13, 18]. Another meta-analysis reported depression to be associated with up to a 52% increased risk of fracture [19]. Whether this is true for bipolar disorder per se is yet to be determined.

Considering the previous research discussing the probable association between unipolar depression and bone, this review would essentially provide a starting point for similar

investigations in bipolar disorder. This review will analyse the existing data, and this information may provide a clearer background into bone fragility associated with bipolar disorder, enabling the details of this association to be further explored.

Objectives

This systematic review will:

1. identify published studies that investigate the association between bipolar disorder and bone health, including BMD and fracture;
2. evaluate the quality of the methodology used in each of the studies eligible for inclusion in this review;
3. collate the evidence, including identifying any potential confounding and/or mediating factors in the association between bipolar disorder and bone health; and
4. provide a comprehensive synthesis of the findings using previously published methodology.

METHODS

Criteria for considering studies for this review

Articles resulting from cross-sectional, case-control and/or longitudinal studies of bone health (defined as BMD, bone quality, osteoporosis and/or fracture), in adult populations (≥18 years) with bipolar disorder (defined by self-report or diagnoses), and inclusive of any sex or nationality, will be considered as eligible for this review.

Grey literature, case studies, theses and conference presentations will be excluded. Baseline data from randomized control trials (RCTs) will be included and treated as cross-sectional analyses.

Search Strategy and Data Extraction

In order to identify the relevant literature, we will undertake an electronic search strategy to investigate research databases from the disciplines of medical, health and the social sciences (PubMed, OVID, CINAHL, Medline). The following medical subject headings (MeSH) will be applied: “bipolar disorder” AND (“bone” OR “osteoporosis” OR “fracture” OR “bone density”), to identify publications that match our eligibility criteria. No limits will be applied

with regards to year of publication. For each database, where appropriate, relevant truncation will be applied. One reviewer will apply the search strategy and identify eligible literature for inclusion by cross-checking with the pre-determined eligibility criteria. Two further reviewers will confirm the eligibility of those identified articles. Professional assistance would be sought to interpret articles written in languages other than English, in order to confirm their relevance to the eligibility criteria. Finally, the reference lists of eligible studies will be hand-searched by two reviewers [20].

Assessment of methodological quality of included articles

The methodological scoring system of Lievense et al [21] will be employed to assess the methodological quality of included articles (Tables 1 and 2). Based on those methodological assessment criteria, each eligible study will be scored, with each study given either a positive or negative score for each criterion. This process of scoring methodological quality reflects cohort studies as the most optimal study design, followed by case-control studies, and finally, cross-sectional study designs. Two reviewers will independently score the methodological quality of each study; should these scores differ, the reviewers will attempt to reconcile any differences, after which a third reviewer would provide final judgement, if necessary. Each study will be ranked according to their total score (%), and deemed as having higher methodological quality if scored above the median, as previously published [22].

Presenting and reporting results

PRISMA-P guidelines [23] will be adhered to with regards to the presentation of findings from this review. Numbers and reasons pertaining to inclusion *vs.* exclusion of papers in context of the predetermined eligibility criteria will be presented in a QUOROM diagram [24]. Key information regarding factors involved in the association between bipolar disorder and bone health will be identified; these factors may include, but will not be limited to inflammatory markers, lifestyle behaviours, socioeconomic status, medications and substance use. Our findings would then be used to reach a consensus as to the link between bipolar disorder and bone.

A meta-analysis is planned, however, if a numerical synthesis is not possible due to methodological heterogeneity, a ‘best evidence synthesis’ will be undertaken. A ‘best

evidence synthesis' would evaluate the level of evidence identified, ranging from no evidence to strong evidence (Table 2), as previously published in the musculoskeletal field [22].

Dissemination

This protocol will be registered with PROSPERO; an international database of health-related systematic review protocols. The findings of our systematic review will be published in a peer-reviewed scientific journal, and results will be shared at national and/or international conferences relevant to the field of bipolar disorder and/or bone health.

Ethics

Since only published data will be used in this systematic review, we do not require ethical permission. However, ethical and governance standards will be strictly adhered to, in matters of data management, and in the presentation and discussion of our results.

Conclusion

To our knowledge, this will be the first systematic review to identify and evaluate the existing evidence-base regarding associations between bipolar disorder and bone health; determining whether any differences exist has both public health and clinical implications. The findings of this review will contribute to existing literature investigating other psychiatric disorders and bone health, and will also provide an evidence-base on which resource allocation and clinical and public health strategies aimed at reducing burden associated with both osteoporosis and bipolar disorder can be founded.

Authors' contributions

All authors conceptualized the research question for this protocol and edited and revised the research question. VC, SLB-O and LW developed the e-search strategy. All authors edited, revised and approved the methodological processes. VC, SLB-O and LJW drafted the manuscript, and all authors edited and contributed to the writing of this paper. All authors read and approved the final version, and guarantee the review.

Funding

The study is supported by the National Health and Medical Research Council (NHMRC), Australia (1104438). VC is supported by a Deakin University Postgraduate Research Scholarship, SLB-O is supported by a NHMRC Career Development Fellowship (1107510), MB is supported by a NHMRC Senior Principal Research Fellowship (1059660) and LJW is supported by a NHMRC Career Development Fellowship (1064272).

Competing interests

None of the authors have any relevant conflicts of interest related to the work under consideration for publication. SLB-O has received speaker fees from Amgen, and Grant/Research support from the University of Melbourne, Deakin University, Arthritis Victoria, Arthritis Australia, Australian Association of Gerontology, and the City of Greater Geelong. JAP has received speaker fees from Amgen, Eli Lilly and Sanofi-Aventis and funding from the Geelong Region Medical Research Foundation, Barwon Health, Perpetual Trustees, The University of Melbourne, Deakin University, ANZ Charitable Trust, the American Society for Bone and Mineral Research, Amgen (Europe) GmBH, the BUPA Foundation, Osteoporosis Australia, Australia and New Zealand Bone and Mineral Society and the NHMRC. MB has received Grant/Research Support from the NIH, Simons Foundation, CRC for Mental Health, Stanley Medical Research Institute, MBF, NHMRC, Beyond Blue, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Organon, Novartis, Mayne Pharma, Servier and Astra Zeneca. He has been a paid consultant for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck and Pfizer and a paid speaker for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Organon, Pfizer, Sanofi Synthelabo, Solvay and Wyeth. LJW has received Grant/Research support from Eli Lilly, Pfizer, The University of Melbourne, Deakin University and the NHMRC.

Table 1 – Criteria list for assessment of study quality, adapted from Lievense et al [21]

Item	Criterion	
Study Population		
1	Uniform point (selection before disease was present)	C/CC/CS
2	Cases and controls drawn from the same population	CC
3	Participation rate >80% for cases/cohort	C/CC/CS
4	Participation rate>80% for controls	CC
Assessment of risk factor		
5	Exposure assessment blinded	C/CC/CS
6	Exposure measured identically for cases and controls	CC
7	Exposure assessed prior to the outcome	C/CC/CS
Assessment of outcome		
8	Bone health assessed identically in patients with bipolar disorder.	C/CC/CS
9	Presence of osteoporosis assessed reproducibly	C/CC/CS
10	Osteoporosis identification assessed according to BMD measurements	C/CC/CS
Study design		
11	Prospective design used	C/CC
12	Follow-up time >24 months	C
13	Withdrawals <20%	C
Analysis and data presentation		
14	Appropriate analysis techniques used	C/CC/CS
15	Adjusted for at least age and sex	C/CC/CS

C, applicable to cohort studies, CC, applicable to case-control studies, CS, applicable to cross-sectional.

Table 2 – Method for determining the level of evidence for best evidence synthesis, adapted from Lievense et al; replicated from Brennan et al [21].

Level of evidence	Criteria for inclusion in best evidence synthesis
Strong evidence	Generally consistent findings in: ▪ Multiple high-quality cohort studies
Moderate evidence	Generally consistent findings in: ▪ 1 high quality cohort study and >2 high quality case-control studies ▪ >3 high quality case-control studies
Limited evidence	Generally consistent findings in: ▪ Single cohort study ▪ 1 or 2 case-control studies or ▪ Multiple cross-sectional studies
Conflicting evidence	Inconsistent findings in >25% of the trials
No evidence	No studies could be found

REFERENCES

1. Merikangas, K.R., Jin R, He JP, Kessler RC, Lee S., Sampson N.A., Viana M.C., Andrade L.H., Hu C., Karam E.G., Ladea M., Medina-Mora M.E., Ono Y., Posada-Villa J., Sagar R., Wells J.E., Zarkov Z., *Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative.* Arch Gen Psychiatry, 2011. **68**(3): p. 241-251.
2. Murray, C.L. and A.D. Lopez, *Summary: Global burden of disease*, in *Global burden of disease and injury series*. 1996, The harvard school of public health, on behalf of the world health organization and the world bank: Boston, MA, USA.
3. Laxman, K.E., K.S. Lovibond, and M.K. Hassan, *Impact of bipolar disorder in employed populations.* Am J Manag Care, 2008. **14**(11): p. 757-64.
4. Fajutrao, L., Locklear, J., Priaulx, L., Heyes, L., *A systematic review of the evidence of the burden of bipolar disorder in Europe.* Clin Pract Epidemiol Ment Health, 2009. **5**: p. 3-3.
5. DE Hert, M., Correll, C.U., Bobes, J., Cetkovich-Bakmas, M., Cohen, D., Asai, I., Detraux, J., Gautam, S., Möller, H.J., Ndetei, D.M., Newcomer, J.W., Uwakwe, R., Leucht, S., *Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care.* World Psychiatry, 2011. **10**(1): p. 52-77.
6. Rizzoli, R., et al., *Antidepressant medications and osteoporosis.* Bone, 2012. **51**(3): p. 606-13.
7. Aloumanis, K., Mavroudis, K., *The "depressive" face of osteoporosis and the "osteoporotic" face of depression.* Hormones (Athens), 2013. **12**(3): p. 350-62.
8. Wade, S.W., Strader, C., Fitzpatrick, L. A., Anthony, M. S., O'Malley, C. D., *Estimating prevalence of osteoporosis: examples from industrialized countries.* Arch Osteoporos, 2014. **9**(1): p. 1-10.
9. *Estimating the prevalence of osteoporosis in Australia*, AIHW, Editor. 2014, Australian Institute of Health and Welfare: Canberra, ACT 2601. p. 16-18.
10. Blume, S.W. and J.R. Curtis, *Medical costs of osteoporosis in the elderly Medicare population.* Osteoporos Int, 2011. **22**(6): p. 1835-44.
11. Watts, J.J., Abimanyi-Ochom, J., Sanders, K.M. *Osteoporosis costing all Australians A new burden of disease analysis – 2012 to 2022*. 2012 04/08/2016]; Available from:

http://www.osteoporosis.org.au/sites/default/files/files/Burden%20of%20Disease%20Analysis%202012-2022.pdf.

12. Fernandes, B.S., Hodge, J.M., Pasco, J.A., Berk, M., Williams, L.J., *Effects of Depression and Serotonergic Antidepressants on Bone: Mechanisms and Implications for the Treatment of Depression.* Drugs Aging, 2016. **33**(1): p. 21-25.
13. Schweiger, J.U., Schweiger, U., Hüppe, M., Kahl, K.G., Greggersen, W., Fassbinder, E., *Bone density and depressive disorder: a meta-analysis.* Brain and Behavior, 2016: p. n/a-n/a.
14. Bruyere, O., Reginster, J.Y., *Osteoporosis in patients taking selective serotonin reuptake inhibitors: a focus on fracture outcome.* Endocrine, 2015. **48**(1): p. 65-8.
15. Yang, J., et al., *Effects of Long-Term Combination Treatment with Valproate and Atypical Antipsychotics on Bone Mineral Density and Bone Metabolism in Premenopausal Patients with Bipolar Disorder: A Preliminary Study.* Psychiatry Investigation, 2011. **8**(3): p. 256-261.
16. Lee, R.H., Lyles, K.W., Colon-Emeric, C., *A review of the effect of anticonvulsant medications on bone mineral density and fracture risk.* Am J Geriatr Pharmacother, 2010. **8**(1): p. 34-46.
17. Mezuk, B., et al., *Anticonvulsant Use, Bipolar Disorder, and Risk of Fracture Among Older Adults in the Veterans Health Administration.* The American Journal of Geriatric Psychiatry, 2010. **18**(3): p. 245-255.
18. Cizza, G., Primma, S., Coyle, M.,Gourgiotis, L., Csako, G., *Depression and osteoporosis: a research synthesis with meta-analysis.* Horm Metab Res, 2010. **42**(7): p. 467-82.
19. Wu, Q., Liu, J., Gallegos-Orozco, J. F., Hentz, J. G., *Depression, fracture risk, and bone loss: a meta-analysis of cohort studies.* Osteoporos Int, 2010. **21**(10): p. 1627-1635.
20. Horsley, T., Dingwall, O., Sampson, M., *Checking reference lists to find additional studies for systematic reviews.* Cochrane Database Syst Rev, 2011(8): p. Mr000026.
21. Lievense, A., Bierma-Zeinstra, S, Verhagen, A, Verhaar, J, Koes, B, *Influence of work on the development of osteoarthritis of the hip: a systematic review.* J Rheumatol, 2001. **28**(11): p. 2520-2528.
22. Brennan, S.L., Pasco J.A., Urquhart, D.M., Oldenburg, B., Hanna, F.S., Wluka, A.E., *The association between urban or rural locality and hip fracture in community-based adults: a systematic review.* J Epidemiol Community Health, 2010. **64**(8): p. 656-665.

23. Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation.* BMJ, 2015. **349**.

24. Moher, D., Cook, D.J., Eastwood, S., Olkin, I., Rennie, D., Stroup, D.F., *Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement.* The Lancet, 1999. **354**(9193): p. 1896-1900.

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
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review PAGE 2 (ABSTRACT);
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 N/A
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author PAGE 1 (TITLE PAGE)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review PAGE 7
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 PAGE 8
Sponsor	5b	Provide name for the review funder and/or sponsor N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol N/A
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known PAGES 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) PAGE 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 PAGE 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 PAGE 5
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 PAGES 5-6
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review PAGE 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) PAGE 3, PAGE 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 PAGE 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 PAGES 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 PAGE 3, PAGE 5
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 PAGE 3, PAGE 6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised PAGES 6-7
	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) PAGE 6
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) PAGES 6-7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned PAGES 6-7
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) PAGE 6

*** 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.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Association between Bipolar Spectrum Disorder and Bone Health: A meta-analysis and systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013981.R1
Article Type:	Protocol
Date Submitted by the Author:	29-Nov-2016
Complete List of Authors:	Chandrasekaran, Vinoomika; Deakin University - Geelong Waterfront Campus, School of Medicine (IMPACT SRC) Brennan, Sharon; Deakin University - Geelong Waterfront Campus, Department of Medicine Stuart, Amanda; Deakin University, Pasco, Julie; The University of Melbourne, Clinical and Biomedical Sciences: Barwon Health Berk, Michael; Deakin University, IMPACT SRC Hodge, Jason; Deakin University - Waurn Ponds Campus, Geelong Centre for Emerging Infectious Diseases (GCEID); Barwon Health, Geelong Centre for Emerging Infectious Diseases (GCEID) Williams, Lana; Deakin University,
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Mental health, Public health
Keywords:	Bipolar Disorder, Bone Health, EPIDEMIOLOGY, Systematic Review Protocol

Association between Bipolar Spectrum Disorder and Bone Health: A meta-analysis and systematic review protocol

Vinoomika Chandrasekaran[1](vchandra@barwonhealth.org.au)

Sharon L Brennan-Olsen[1,2,3,4] (sbrennan@unimelb.edu.au)

Amanda L Stuart[1] (amandh@barwonhealth.org.au)

Julie A Pasco[1,2] (juliep@barwonhealth.org.au)

Michael Berk[1,5,6,7,8] (mikebe AT barwonhealth.org.au)

Jason M Hodge[1,8] (jasonh@barwonhealth.org.au)

Lana J Williams[1] (lanaw@barwonhealth.org.au)

[1]*Deakin University, Geelong, Australia*
[2]*Australian Institute for Musculoskeletal Science (AIMSS), The University of Melbourne and Western Health, St Albans, Australia*
[3]*Department of Medicine, The University of Melbourne-Western Precinct, St Albans, Australia*
[4]*Institute for Health and Ageing, Australian Catholic University, Melbourne, Australia*
[5]*Department of Psychiatry, University of Melbourne, Parkville, Australia*
[6]*Florey Institute of Neuroscience and Mental Health, Parkville, Australia*
[7]*Orygen the National Centre of Excellence in Youth Mental Health, Parkville, Australia*
[8]*Barwon Health University Hospital, Geelong, Australia*

Author for correspondence:

Dr Lana Williams

Deakin University

School of Medicine

IMPACT Strategic Research Centre

PO Box 281, Geelong 3220, Australia

Tel: +61 3 4215 3303 Fax +61 3 4215 3491

Email: lanaw@barwonhealth.org.au

Word count: Manuscript: 2080; Abstract: 234

Keywords: bipolar spectrum disorder, bone, osteoporosis, fracture, systematic review, meta-analysis

Abstract

Introduction:

Bipolar Spectrum Disorder is a chronic, episodic illness, associated with significant personal, social and economic burden. It is estimated to affect approximately 2.4% of the population worldwide and is commonly associated with psychological and/or physiological comorbidities. Osteoporosis is one such comorbidity; a disease of bone that is asymptomatic until a fracture occurs. This systematic review attempts to capture, collate, assess and discuss the literature investigating the association between bipolar spectrum disorder and bone health.

Methods and analysis:

We aim to identify articles that investigate the association between bipolar spectrum disorder and bone health in adults by systematically searching the Medline, PubMed, OVID and CINAHL databases. Two independent reviewers will determine eligibility of studies according to pre-determined criteria, and methodological quality will be assessed using a previously published scoring system. A meta-analysis will be conducted, and statistical methods will be used to identify and control for heterogeneity, if possible. If numerical syntheses are prevented due to statistical heterogeneity, a best evidence synthesis will be conducted to assess the level of evidence for associations between bipolar spectrum disorder and bone health.

Ethics and dissemination:

Ethical permission will not be required for this systematic review since only published data will be used. This protocol will be registered with PROSPERO. Findings of the review will be published in a peer-reviewed scientific journal, and will be presented to clinical and population health audiences at national and international conferences.

Strengths and limitations of this study:

- This systematic review will explore a novel and covert clinical area.
- It will comprehensively assess existing literature that investigates associations between bipolar spectrum disorder and bone health.
- Potential confounders and/or mediators of the relationship will be identified.
- Two authors will independently confirm study selection, and undertake data extraction and methodological assessment.
- A potential limitation of this review may be the paucity of data available due to this being a nascent area of enquiry, and that there may be much heterogeneity in available studies.

INTRODUCTION

Bipolar spectrum disorder, a mental disorder characterised by biphasic fluctuations in mood, is a severe, chronic, episodic illness, which generally necessitates pharmacotherapy and/or psychotherapy. It is estimated to affect approximately 2.4% of the population [1] and has been ranked the sixth leading cause of disability in the world, amongst individuals aged 15-44 years [2]. The related direct and indirect costs associated with bipolar spectrum disorder are substantial [3, 4]. The burden of bipolar spectrum disorder is experienced on many levels – by the sufferer, their immediate family and friends and also by the healthcare system. Symptom burden and disease course is often worsened in the presence of psychological and/or physiological comorbidities [5, 6].

Psychiatric disorders, including bipolar spectrum disorder, have been associated with early mortality, with approximately 60% of this excess mortality due to chronic physical illness [7]. A particularly common comorbidity of unipolar depression is osteoporosis [8, 9]. Yet it is normatively overlooked, due to being asymptomatic until fracture occurs. Osteoporosis is a global public health issue, estimated to affect nearly 49 million individuals in industrialised countries, with this on the rise as a consequence of the ageing population. [10, 11]. The rising global economic burden, related to the direct and indirect costs of medical care and rehabilitation of individuals with osteoporotic fractures is concerning [12, 13]. Both clinically diagnosed unipolar depression and depressive symptoms have been shown to be associated with deficits in bone mineral density (BMD), bone loss over time and increased fracture risk in both, men and women [9, 14, 15]. Furthermore, antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs) used in treatment of depression have also been shown to be noxious to bone [16]. Other psychotropic medication, namely antipsychotics and anticonvulsants have also been shown to have a deleterious effect on bone [17-19]. A recent research synthesis with meta-analyses concluded that depression should be considered a serious risk factor for osteoporosis, based on aggregated data showing BMD among individuals with depression to be up to 7.3% lower [15, 20]. Another meta-analysis reported depression to be associated with up to a 52% increased risk of fracture [21]. Whether this is true for bipolar spectrum disorder per se is yet to be determined.

Considering the previous research discussing the probable association between unipolar depression and bone, this review would essentially provide a starting point for similar

investigations in bipolar spectrum disorder. This review will analyse the existing data, and this information may provide a clearer background into bone fragility associated with bipolar spectrum disorder, enabling the details of this association to be further explored.

Objectives

This systematic review will:

1. identify published studies that investigate the association between bipolar spectrum disorder and bone health, including BMD and fracture;
2. evaluate the quality of the methodology used in each of the studies eligible for inclusion in this review;
3. collate the evidence, including identifying any potential confounding and/or mediating factors in the association between bipolar spectrum disorder and bone health;
4. perform sensitivity analyses to account for differences between (i) self-reported and diagnosed bipolar spectrum disorder, (ii) diagnostic criteria between versions of the DSM and/or ICD, and (iii) bipolar disorders I and II; and
5. provide a comprehensive synthesis of the findings using previously published methodology.

METHODS

Criteria for considering studies for this review

Articles resulting from cross-sectional, case-control and/or longitudinal studies of bone health (defined as BMD, bone quality, osteoporosis and/or fracture), in adult populations (≥18 years) with bipolar spectrum disorder (defined by self-report, medical records or diagnoses based on any version of the Diagnostic and Statistical Manual of Mental Disorders or International Statistical Classification of Diseases and Related Health Problems criteria), inclusive of any sex or nationality, and published in any year, will be considered as eligible for this review.

Grey literature, case studies, theses and conference presentations will be excluded. Baseline data from randomized control trials (RCTs) will be included and treated as cross-sectional analyses.

Search Strategy and Data Extraction

In order to identify the relevant literature, we will undertake an electronic search strategy to investigate research databases from the disciplines of medical, health and the social sciences (PubMed, OVID, CINAHL, Medline). The following medical subject headings (MeSH) will be applied: "bipolar disorder" AND ("bone" OR "osteoporosis" OR "fracture" OR "bone density"), to identify publications that match our eligibility criteria. For our search strategy, we will also include the key word term of 'bipolar spectrum disorder'.

No limits will be applied with regards to year of publication. For each database, where appropriate, relevant truncation will be applied. One reviewer will apply the search strategy and identify eligible literature for inclusion by cross-checking with the pre-determined eligibility criteria. Two further reviewers will confirm the eligibility of those identified articles. Professional assistance would be sought to interpret articles written in languages other than English, in order to confirm their relevance to the eligibility criteria. Finally, the reference lists of eligible studies will be hand-searched by two reviewers [22].

Assessment of methodological quality of included articles

The methodological scoring system of Lievense et al [23] will be employed to assess the methodological quality of included articles (Tables 1 and 2). Based on those methodological assessment criteria, each eligible study will be scored, with each study given either a positive or negative score for each criterion. This process of scoring methodological quality reflects cohort studies as the most optimal study design, followed by case-control studies, and finally, cross-sectional study designs. Two reviewers will independently score the methodological quality of each study; should these scores differ, the reviewers will attempt to reconcile any differences, after which a third reviewer would provide final judgement, if necessary. Each study will be ranked according to their total score (%), and deemed as having higher methodological quality if scored above the median, as previously published [24].

For the meta-analyses we will determine the population with bipolar spectrum disorder to be our proxy 'treatment' group and apply the Hunter-Schmidt's approach [25], whereby a pooled within-group standard deviation will be used. Effect size will be corrected for measurement error by dividing the effect size by the square root of the reliability coefficient

of the dependent variable: whereby measurement error correction equals the effect size divided by the square root of r.

Presenting and reporting results

PRISMA guidelines [26] will be adhered to with regards to the presentation of findings from this review, and this protocol adheres to the PRISMA-P guidelines [27]. Numbers and reasons pertaining to inclusion *vs.* exclusion of papers in context of the predetermined eligibility criteria will be presented in a QUOROM diagram [28]. Key information regarding factors involved in the association between bipolar spectrum disorder and bone health will be identified; these factors may include, but will not be limited to inflammatory markers, lifestyle behaviours, socioeconomic status, medications and substance use. Our findings will be useful to inform and reach a consensus as to the link between bipolar spectrum disorder and bone health.

A meta-analysis is planned, however, if a numerical synthesis is not possible due to methodological heterogeneity, a 'best evidence synthesis' will be undertaken. A 'best evidence synthesis' would evaluate the level of evidence identified, ranging from no evidence to strong evidence (Table 2), as previously published in the musculoskeletal field [24].

We will also perform sensitivity analyses to account for differences between (i) self-reported and diagnosed bipolar spectrum disorder, (ii) diagnostic criteria between versions of the DSM and/or ICD, and (iii) bipolar disorders I and II.

Dissemination

This protocol will be registered with PROSPERO; an international database of health-related systematic review protocols. The findings of our systematic review will be published in a peer-reviewed scientific journal, and results will be shared at national and/or international conferences relevant to the field of bipolar spectrum disorder and/or bone health.

Ethics

Since only published data will be used in this systematic review, we do not require ethical permission. However, ethical and governance standards will be strictly adhered to, in matters of data management, and in the presentation and discussion of our results.

Conclusion

To our knowledge, this will be the first systematic review to identify and evaluate the existing evidence-base regarding associations between bipolar spectrum disorder and bone health; and determining the nature of this relationship has both public health and clinical implications. The findings of this review will contribute to existing literature investigating other psychiatric disorders and bone health, and will also provide an evidence-base on which resource allocation and clinical and public health strategies aimed at reducing burden associated with both osteoporosis and bipolar spectrum disorder can be founded.

Authors' contributions

All authors conceptualized the research question for this protocol and edited and revised the research question. VC, SLB-O and LW developed the e-search strategy. All authors edited, revised and approved the methodological processes. VC, SLB-O and LJW drafted the manuscript, and all authors edited and contributed to the writing of this paper. All authors read and approved the final version, and guarantee the review.

Funding

The study is supported by the National Health and Medical Research Council (NHMRC), Australia (1104438). VC is supported by a Deakin University Postgraduate Research Scholarship, SLB-O is supported by a NHMRC Career Development Fellowship (1107510), MB is supported by a NHMRC Senior Principal Research Fellowship (1059660) and LJW is supported by a NHMRC Career Development Fellowship (1064272).

Competing interests

None of the authors have any relevant conflicts of interest related to the work under consideration for publication. SLB-O has received speaker fees from Amgen, and Grant/Research support from the University of Melbourne, Deakin University, Arthritis Victoria, Arthritis Australia, Australian Association of Gerontology, and the City of Greater Geelong. JAP has received speaker fees from Amgen, Eli Lilly and Sanofi-Aventis and funding from the Geelong Region Medical Research Foundation, Barwon Health, Perpetual Trustees, The University of Melbourne, Deakin University, ANZ Charitable Trust, the

American Society for Bone and Mineral Research, Amgen (Europe) GmbH, the BUPA Foundation, Osteoporosis Australia, Australia and New Zealand Bone and Mineral Society and the NHMRC. MB has received Grant/Research Support from the NIH, Simons Foundation, CRC for Mental Health, Stanley Medical Research Institute, MBF, NHMRC, Beyond Blue, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Organon, Novartis, Mayne Pharma, Servier and Astra Zeneca, and he has been a paid consultant for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck and Pfizer and a paid speaker for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Organon, Pfizer, Sanofi Synthelabo, Solvay and Wyeth. LJW has received Grant/Research support from Eli Lilly, Pfizer, The University of Melbourne, Deakin University and the NHMRC.

Table 1 – Criteria list for assessment of study quality, adapted from Lievense et al [23].

Item	Criterion	
Study Population		
1	Uniform point (selection before disease was present)	C/CC/CS
2	Cases and controls drawn from the same population	CC
3	Participation rate >80% for cases/cohort	C/CC/CS
4	Participation rate>80% for controls	CC
Assessment of risk factor		
5	Exposure assessment blinded	C/CC/CS
6	Exposure measured identically for cases and controls	CC
7	Exposure assessed prior to the outcome	C/CC/CS
Assessment of outcome		
8	Bone health assessed identically in patients with bipolar spectrum disorder.	C/CC/CS
9	Presence of osteoporosis assessed reproducibly	C/CC/CS
10	Osteoporosis identification assessed according to BMD measurements	C/CC/CS
Study design		
11	Prospective design used	C/CC
12	Follow-up time >24 months	C
13	Withdrawals <20%	C
Analysis and data presentation		
14	Appropriate analysis techniques used	C/CC/CS
15	Adjusted for at least age and sex	C/CC/CS

C, applicable to cohort studies, CC, applicable to case-control studies, CS, applicable to cross-sectional.

Table 2 – Method for determining the level of evidence for best evidence synthesis, adapted from Lievense et al; replicated from Brennan et al [24]

Level of evidence	Criteria for inclusion in best evidence synthesis
Strong evidence	Generally consistent findings in: ▪ Multiple high-quality cohort studies
Moderate evidence	Generally consistent findings in: ▪ 1 high quality cohort study and >2 high quality case-control studies ▪ >3 high quality case-control studies
Limited evidence	Generally consistent findings in: ▪ Single cohort study ▪ 1 or 2 case-control studies or ▪ Multiple cross-sectional studies
Conflicting evidence	Inconsistent findings in >25% of the trials
No evidence	No studies could be found

REFERENCES

1. Merikangas, K.R., Jin R, He JP, Kessler RC, Lee S., Sampson N.A., Viana M.C., Andrade L.H., Hu C., Karam E.G., Ladea M., Medina-Mora M.E., Ono Y., Posada-Villa J., Sagar R., Wells J.E., Zarkov Z., *Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative.* Arch Gen Psychiatry, 2011. **68**(3): p. 241-251.
2. Murray, C.L. and A.D. Lopez, *Summary: Global burden of disease*, in *Global burden of disease and injury series*. 1996, The harvard school of public health, on behalf of the world health organization and the world bank: Boston, MA, USA.
3. Laxman, K.E., K.S. Lovibond, and M.K. Hassan, *Impact of bipolar disorder in employed populations.* Am J Manag Care, 2008. **14**(11): p. 757-64.
4. Fajutrao, L., Locklear, J., Priaulx, L., Heyes, L., *A systematic review of the evidence of the burden of bipolar disorder in Europe.* Clin Pract Epidemiol Ment Health, 2009. **5**: p. 3-3.
5. Forty, L., et al., *Comorbid medical illness in bipolar disorder.* The British Journal of Psychiatry, 2014. **205**(6): p. 465-472.
6. Parker, G.B., *Comorbidities in bipolar disorder: models and management.* Med J Aust 2010. **193**(4): p. 18.
7. DE Hert, M., Correll, C.U., Bobes, J., Cetkovich-Bakmas, M., Cohen, D., Asai, I., Detraux, J., Gautam, S., Möller, H.J., Ndetei, D.M., Newcomer, J.W., Uwakwe, R., Leucht, S., *Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care.* World Psychiatry, 2011. **10**(1): p. 52-77.
8. Rizzoli, R., et al., *Antidepressant medications and osteoporosis.* Bone, 2012. **51**(3): p. 606-13.
9. Aloumanis, K., Mavroudis, K., *The "depressive" face of osteoporosis and the "osteoporotic" face of depression.* Hormones (Athens), 2013. **12**(3): p. 350-62.
10. Wade, S.W., Strader, C., Fitzpatrick, L. A., Anthony, M. S., O'Malley, C. D., *Estimating prevalence of osteoporosis: examples from industrialized countries.* Arch Osteoporos, 2014. **9**(1): p. 1-10.
11. *Estimating the prevalence of osteoporosis in Australia*, AIHW, Editor. 2014, Australian Institute of Health and Welfare: Canberra, ACT 2601. p. 16-18.

12. Blume, S.W. and J.R. Curtis, *Medical costs of osteoporosis in the elderly Medicare population.* Osteoporos Int, 2011. **22**(6): p. 1835-44.

13. Watts, J.J., Abimanyi-Ochom, J., Sanders, K.M. *Osteoporosis costing all Australians A new burden of disease analysis – 2012 to 2022*. 2012 04/08/2016]; Available from: http://www.osteoporosis.org.au/sites/default/files/files/Burden%20of%20Disease%20Analysis%202012-2022.pdf.

14. Fernandes, B.S., Hodge, J.M., Pasco, J.A., Berk, M., Williams, L.J., *Effects of Depression and Serotonergic Antidepressants on Bone: Mechanisms and Implications for the Treatment of Depression.* Drugs Aging, 2016. **33**(1): p. 21-25.

15. Schweiger, J.U., Schweiger, U., Hüppe, M., Kahl, K.G., Greggersen, W., Fassbinder, E., *Bone density and depressive disorder: a meta-analysis.* Brain and Behavior, 2016: p. n/a-n/a.

16. Bruyere, O., Reginster, J.Y., *Osteoporosis in patients taking selective serotonin reuptake inhibitors: a focus on fracture outcome.* Endocrine, 2015. **48**(1): p. 65-8.

17. Yang, J., et al., *Effects of Long-Term Combination Treatment with Valproate and Atypical Antipsychotics on Bone Mineral Density and Bone Metabolism in Premenopausal Patients with Bipolar Disorder: A Preliminary Study.* Psychiatry Investigation, 2011. **8**(3): p. 256-261.

18. Lee, R.H., Lyles, K.W., Colon-Emeric, C., *A review of the effect of anticonvulsant medications on bone mineral density and fracture risk.* Am J Geriatr Pharmacother, 2010. **8**(1): p. 34-46.

19. Mezuk, B., et al., *Anticonvulsant Use, Bipolar Disorder, and Risk of Fracture Among Older Adults in the Veterans Health Administration.* The American Journal of Geriatric Psychiatry, 2010. **18**(3): p. 245-255.

20. Cizza, G., Primma, S., Coyle, M.,Gourgiotis, L., Csako, G., *Depression and osteoporosis: a research synthesis with meta-analysis.* Horm Metab Res, 2010. **42**(7): p. 467-82.

21. Wu, Q., Liu, J., Gallegos-Orozco, J. F., Hentz, J. G., *Depression, fracture risk, and bone loss: a meta-analysis of cohort studies.* Osteoporos Int, 2010. **21**(10): p. 1627-1635.

22. Horsley, T., Dingwall, O., Sampson, M., *Checking reference lists to find additional studies for systematic reviews.* Cochrane Database Syst Rev, 2011(8): p. Mr000026.

23. Lievense, A., Bierma-Zeinstra, S, Verhagen, A, Verhaar, J, Koes, B, *Influence of work on the development of osteoarthritis of the hip: a systematic review.* J Rheumatol, 2001. **28**(11): p. 2520-2528.

24. Brennan, S.L., Pasco J.A., Urquhart, D.M., Oldenburg, B., Hanna, F.S., Wluka, A.E., *The association between urban or rural locality and hip fracture in community-based adults: a systematic review.* J Epidemiol Community Health, 2010. **64**(8): p. 656-665.

25. Montgomery, G.H., *Hunter, John E., & Schmidt, Frank L. (1990). Methods of Meta-Analysis: Correcting Error and Bias in Research Findings. Newbury Park, CA: Sage, 592 Pages, $38.00 (Paper).* American Journal of Clinical Hypnosis, 2000. **43**(1): p. 81-82.

26. Moher, D., et al., *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.* PLoS Med, 2009. **6**(7): p. e1000097.

27. Shamseer, L., Moher, D., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation.* BMJ, 2015. **349**.

28. Moher, D., Cook, D.J., Eastwood, S., Olkin, I., Rennie, D., Stroup, D.F., *Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement.* The Lancet, 1999. **354**(9193): p. 1896-1900.

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
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review PAGE 2 (ABSTRACT);
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 N/A
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author PAGE 1 (TITLE PAGE)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review PAGE 8 (Paragraph 2)
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 PAGE 8 (Paragraph 3)
Sponsor	5b	Provide name for the review funder and/or sponsor N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol N/A
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known PAGES 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) PAGE 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 PAGE 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 PAGE 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 PAGES 6-7
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review PAGE 6-7

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) PAGE 3, PAGES 6-7
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 PAGES 6-7
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 PAGE 5 (Criteria), PAGE 6 (Paragraphs 1, 2 and 4),
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale PAGE 5 (Objectives) PAGE 7 (Paragraphs 2 and 3)
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 PAGE 3, PAGE 6
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised PAGES 6-7
	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) PAGE 6-7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) PAGES 6-7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned PAGES 6-7
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) PAGE 6-7

*** 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.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.