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# BMJ Open Bone health in bipolar disorder: a study protocol for a case-control study in Australia

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## ABSTRACT

**Introduction** Little is known about the bone health of adults with bipolar disorder, aside from evidence purporting bone deficits among individuals with other mental illnesses, or those taking medications commonly used in bipolar disorder. In this paper, we present the methodology of a case-control study which aims to examine the role of bipolar disorder as a risk factor for bone fragility.

**Methods and analysis** Men and women with bipolar disorder (~200 cases) will be recruited and compared with participants with no history of bipolar disorder (~1500 controls) from the Geelong Osteoporosis Study. Both cases and controls will be drawn from the Barwon Statistical Division, south-eastern Australia. The Structured Clinical Interview for DSM-IV-TR Research Version, Non-patient edition is the primary diagnostic instrument, and psychiatric symptomatology will be assessed using validated rating scales. Demographic information and detailed lifestyle data and medical history will be collected via comprehensive questionnaires. Participants will undergo dual energy X-ray absorptiometry scans and other clinical measures to determine bone and body composition. Blood samples will be provided after an overnight fast and stored for batch analysis.

**Ethics and dissemination** Ethics approval has been granted from Barwon Health Research Ethics Committee. Participation in the study is voluntary. The study findings will be disseminated via peer-reviewed publications, conference presentations and reports to the funding body.

## INTRODUCTION

Bipolar disorder, estimated to affect around 2.5% of the adult population, is a chronic, recurrent condition, characterised by biphasic fluctuations in mood.<sup>1</sup> Psychiatric comorbidity is common, often complicating diagnoses, management and prognosis, and the risk of early mortality is increased.<sup>2</sup> Bipolar disorder is also a top 10 cause of years lost due to disability,<sup>3</sup> with this reflecting the nature of the course and early onset age. As such, the related direct and indirect costs associated with bipolar disorder are notable.

## Strengths and limitations of this study

- This case-control study will explore a novel and covert clinical area.
- Both cases and controls will be drawn from the same population.
- A large number of potential confounders will be available for testing in statistical models.
- As with all observational studies, results could be biased by unrecognised confounding and may not be generalisable to other populations.

Aside from psychiatric comorbidities, medical comorbidities are also burdensome. Individuals with bipolar disorder are at increased risk of most disease groups, for example cardiovascular, metabolic, gastrointestinal and pulmonary disease, with such relationships having associated excess mortality.<sup>4</sup> Research is now emerging to suggest that poor bone health is yet another potential comorbidity.<sup>5,6</sup> Both clinically diagnosed unipolar depression and depressive symptoms have been associated with deficits in bone mineral density (BMD) and increases in fracture risk in both men and women across the adult age range,<sup>7-10</sup> as has schizophrenia,<sup>11</sup> alcohol use<sup>12</sup> and eating disorders.<sup>13</sup> Furthermore, psychotropic agents commonly used in the treatment of bipolar disorder (antidepressants, antipsychotics and anticonvulsants), have each been shown to be independently detrimental to bone.<sup>14-16</sup>

In essence, very little is known about the relationship between bipolar disorder and bone health and the factors involved, apart from what can be implied from other psychiatric disorders. An understanding of the influence of other factors in the relationship of interest is also needed. These include lifestyle factors such as smoking, alcohol, diet and habitual physical activity, socioeconomic status, prescription drug use



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especially psychotropic agents, medical and psychiatric comorbidity and biomarkers of common risk, such as systemic inflammatory and oxidative stress markers. In this paper, we present the methodology of a case-control study which aims to examine the role of bipolar disorder as a risk factor for bone fragility. Specifically, we aim to assess:

1. The association between bipolar disorder and parameters of bone health including BMD, bone quality and markers of bone turnover.
2. Whether relationships are explained by specific biological, lifestyle and social factors.

## METHOD

### Study design and setting

This case-control study aims to recruit men and women with bipolar disorder (cases) and use data from peers with no history of bipolar disorder (controls) participating in the Geelong Osteoporosis Study (GOS). Both cases and controls will be drawn from the Barwon Statistical Division (BSD), a geographically well-defined region of south-eastern Australia. The project commenced in 2011 and will be completed in 2020.

### Sampling

#### Cases

Men and women with bipolar disorder attending public and/or private healthcare settings within the BSD will be approached to participate. The study will be advertised through the media and all healthcare settings in the region. To be considered for inclusion in this study, participants are required to be aged 20 years or over, have the capacity to consent to participation in the study and to follow its instructions and procedures and meet criteria for a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) diagnosis of bipolar I, II disorder or not otherwise specified (NOS).

#### Controls

Controls will be drawn from a large cohort study. The GOS involves a population-based sample of women and men randomly selected from electoral rolls for the BSD. Originally developed to investigate the epidemiology of osteoporosis, the GOS was expanded to examine psychiatric illness and other common diseases.

During 1994–1997, an age-stratified, random, population-based sample of 1494 women spanning the full adult age range was recruited. In 2001, the male arm of the GOS commenced, comprising a sample of 1540 men aged 20–93 years. Male and female control participants with no history of bipolar disorder will be drawn from the most recent follow-up phases of the GOS. Further comprehensive details regarding sampling, recruitment, methodology and outcomes of the GOS are published elsewhere.<sup>17</sup>

## Measures

A listing of psychiatric assessments, clinical measures, biochemical and questionnaire data to be collected is presented in [table 1](#).

### Psychiatric assessments

The Structured Clinical Interview for DSM-IV-TR Research Version, Non-patient edition (SCID-I/NP) is the primary diagnostic instrument administered to both the cases and controls. This is a validated, semistructured clinical interview for the major axis I psychiatric disorders in the DSM-IV-TR.<sup>18</sup> Assessments focus on depressive disorders including bipolar disorder (I, II, NOS), major depressive disorder, minor depression, dysthymia, mood disorder due to a general medical condition and substance-induced mood disorder; anxiety disorders including panic disorders, agoraphobia, social phobia, specific phobia, post-traumatic stress disorder, obsessive compulsive disorder, generalised anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder and anxiety disorder NOS; substance use disorders and eating disorders. Information regarding date of onset, frequency, duration and chronicity of episodes will also be collected. The presence of personality disorders including paranoid, schizoid, schizotypal, histrionic, narcissistic, borderline, antisocial, avoidant, dependent and obsessive-compulsive will be assessed using the SCID-II.<sup>19</sup> All clinical interviews will be conducted by trained personnel with postgraduate qualifications in psychology, under the supervision of a clinically trained psychologist.

Bipolar Depression Rating Scale (BDRS)<sup>20</sup> and Young Mania Rating Scale (YMRS)<sup>21</sup> will be used to assess symptoms of depression and mania associated with bipolar disorder. Participants are required to be euthymic at the time of study assessment, denoted by a score of <16 on the BDRS and <14 on the YMRS.

Mood and anxiety symptomatology will be assessed for all participants using the Hospital Anxiety and Depression rating Scale (HADS), a validated, self-report tool used for assessing clinically significant depression or anxiety in a range of clinical and research settings.<sup>22</sup> The HADS consists of seven items for depression (HADS-D) and seven items for anxiety (HADS-A), each with a four-point ordinal scale to describe symptom severity from 0 to 3.

### Sociodemographics

Country of birth, ethnicity, education, marital status, housing and employment status and financial support will be self-reported. Occupation type will be categorised according to the Australian and New Zealand Standard Classification of Occupations, Version 1.2,<sup>23</sup> a classification based on skill level and specialisation. Area-based rankings of relative socioeconomic advantage in terms of access to material and social resources will be derived by linking the residential address for each individual to the corresponding Australian Bureau of Statistics (ABS) Census Collection District, and ABS software used to

**Table 1** Psychiatric assessments, clinical measures, biochemical and questionnaire data collected from both case and control participants

Variable	Instrument
<b>Psychiatric assessments</b>	
Mood, anxiety, substance and eating disorders	Structured Clinical Interview for DSM-IV-TR Research Version, Non-patient edition
Personality disorders	Structured Clinical Interview for DSM-IV Axis II personality disorders
Depression symptoms*	Bipolar Depression Rating Scale
Mania symptoms*	Young Mania Rating Scale
Mood and anxiety symptoms	Hospital Anxiety Depression Scale
<b>Sociodemographics</b>	
Country of birth	Self-report
Ethnicity	Self-report
Education level	Self-report
Marital status	Self-report
Housing status	Self-report
Employment status	Self-report
Financial support	Self-report
Occupation	Australian and New Zealand Standard Classification of Occupations, Version 1.2
Socioeconomic status	Socio-Economic Indexes for Areas
<b>Lifestyle</b>	
Diet and alcohol consumption	Cancer Council of Victoria Dietary Questionnaire for Epidemiological Studies
Smoking	Self-report
Physical activity	The Baecke Measurement of Habitual Activity Physical activity scale for the elderly
Quality of Life	WHO Quality of Life Scale (WHOQOL-BREF)
General Health	Self-report
Social support	Multidimensional Scale of Perceived Social Support
<b>Clinical measures</b>	
Blood pressure	Digital blood pressure meter
Hand grip strength	Hand-held dynamometer (Jamar, Sammons Preston, Bolingbrook, IL).
<b>Medical history</b>	
Medical conditions	Self-report

Continued

**Table 1** Continued

Variable	Instrument
Medication use	Self-report
Reproductive history	Self-report
Fracture history	Self-report
Falls history	Self-report
<b>Pain and somatic symptoms</b>	
Pain	Visual analogue scale The Foot Disability Questionnaire Chronic Back Pain Grade Questionnaire
Somatic symptoms	The Patient Health Questionnaire-15
<b>Bone and body composition</b>	
Weight	Electronic scales
Height	Stadiometer
Bone mineral density and body fat distribution	Dual energy X-ray absorptiometry scans (Prodigy; GE Lunar, Madison, Wisconsin, USA)
Bone quality	Quantitative calcaneal ultrasound (Achilles InSight; GE Lunar, Madison, Wisconsin, USA)
<b>Biochemistry</b>	
Interleukin 6	ELISAs (R&D Systems)
Total antioxidant capacity	ELISAs (R&D Systems)
C-telopeptide	ELISAs (USCN Life Sciences)
Amino-terminal propeptide of type I procollagen (PINP)	ELISAs (USCN Life Sciences)
Vitamin D <sub>3</sub>	ELISAs (R&D Systems)

\*Cases only.

derive the Socio-Economic Index For Areas scores, providing a set of summary indexes that indicate relative socio-economic advantage or disadvantage at the small area level.<sup>24 25</sup>

#### Lifestyle data

The Cancer Council of Victoria Dietary Questionnaire for Epidemiological Studies (DQES)<sup>26</sup> will be used to assess consumption of food and alcohol. The DQES notes consumption of 74 foods and six alcoholic beverages over the preceding 12 months using a 10-point frequency scale.

Smoking (current and past patterns of tobacco smoking included manufactured and 'hand-rolled' cigarettes, cigars and pipes) will be gathered by self-report.

Physical activity will be measured using validated questionnaires (Baecke Measurement of Habitual Activity<sup>27</sup> and the Physical Activity Scale for the elderly),<sup>28</sup> designed to capture three components of habitual activity,

including physical activity at work, sport during leisure time and physical activity during leisure time excluding sport.

Quality of life (QOL) will be measured using the WHO QOL Scale (WHOQOL-BREF),<sup>29</sup> a shortened version of the WHOQOL-100. The WHOQOL-BREF consists of four QOL domains: physical health, psychological health, social relationships and environment.

Self-reported general health will be determined from the question, 'In general, would you say your health is: excellent, very good, good, fair or poor?'

Perceived social support will be measured using the Multidimensional Scale of Perceived Social Support,<sup>30</sup> designed to measure support from family, friends and significant others.

### Clinical measures

Blood pressure and pulse rate will be observed using a digital meter with the participant seated. Hand grip strength will be measured using a hand-held dynamometer (Jamar, Sammons Preston, Bolingbrook, IL).

### Medical history

Lifetime history of medical conditions will be obtained by self-report. We will obtain each participant's consent to access their medical records and/or contact their medical practitioners to confirm self-reported conditions. Information regarding immunisation records, reproductive history and falls/fracture history will be ascertained by self-report.

Past and current medication use will be self-reported. Participants will be asked to bring in a list of medications or containers to assist with accurate recording of details.

### Pain and somatic symptoms

Pain will be assessed using the Visual Analogue Scale for pain<sup>31</sup>; a validated, self-report tool used for assessing pain severity during the past week. It includes six separate items that yield a rating for overall pain severity, head pain (headaches), back pain, shoulder pain, interference with daily activities and time in pain while awake. The presence of arm, hand, leg, foot, face, stomach and chest pain will also be documented. The Foot Disability Questionnaire<sup>32</sup> and the Chronic Back Pain Grade Questionnaire<sup>33,34</sup> will also afford detailed information regarding foot and back pain.

The Patient Health Questionnaire-15<sup>35</sup> is a validated, self-report somatic symptom subscale derived from the full version of the Patient Health Questionnaire, a self-administrated version of the Primary Care Evaluation of Mental Disorders diagnostic instrument for psychiatric disorders, which assesses 15 somatic symptoms.

### Bone and body composition

Body weight and height will be measured to the nearest 0.1 kg and 0.1 cm, respectively.

Dual energy X-ray absorptiometry scans of the spine (posteroanterior projection, L2-4), proximal femur, total body and forearm sites (ultradistal and distal 33%)

will be conducted using a GE-Lunar Prodigy (Madison, Wisconsin, USA) to determine areal BMD (aBMD, g/cm<sup>2</sup>). Body fat distribution, body fat mass and lean mass will be determined from total body scans.

Bone quality will be determined by quantitative calcaneal ultrasound using an ultrasonometer (GE-Lunar Achilles InSight, Madison, Wisconsin, USA) that provides measures of speed of sound, broadband ultrasound attenuation and stiffness index.

### Biochemistry

A morning blood sample will be collected following an overnight fast and stored at -80°C. Batch analyses will be conducted at the end of the recruitment phase. Serum/plasma will be analysed initially for markers of bone turnover, inflammation and oxidative stress.

### Sample size

The statistical analysis will compare data for cases and controls. Based on a power of 80%, statistical significance at the 0.05 level and previous work,<sup>36</sup> calculations suggest we require 200 cases to detect a difference of at least 7% in BMD at the hip.

### Statistical analyses

Differences in characteristics between cases and controls will be determined using t-tests, Mann-Whitney and  $\chi^2$  analyses, where appropriate. The association between bipolar disorder and bone fragility (BMD, bone quality or biomarkers) will be explored using multiple regression techniques. The analyses will be stratified by sex. Age, weight, height, smoking status, activity level, sociodemographic factors, calcium intake, alcohol consumption, vitamin D levels, other psychiatric disorders, biomarkers and medications known to influence bone metabolism positively (hormone therapy, bisphosphonates, lithium) and negatively (corticosteroids, anticonvulsants, antipsychotics and antidepressants) will be tested in the statistical models as potential confounders or effect modifiers.

### Ethics and dissemination

Participation in the study is voluntary and written informed consent will be obtained from all participants. Data are stored on the mainframe computer of Barwon Health in password protected databases that are backed up daily from the file server. Entry of new data is performed daily, enabling the maintenance of a current, up-to-date database. Findings from this study will be disseminated via peer-reviewed publications, conference presentations and reports to the funding body. Additionally, a summary of findings will be provided to participants on the completion of the study.

## DISCUSSION

The relationship between bipolar disorder and bone health remains relatively unexplored, with obvious and major public health implications. This case-control study will address important questions regarding the interface

of bipolar disorder and bone fragility, capturing information on a range of critical covariates including biomarkers, medication use and lifestyle factors. Furthermore, this study will provide valuable insight into the lifestyle factors associated with bipolar disorder and the medical consequences at a population level. The biomarker component of the study will further allow an understanding of the role of inflammatory and oxidative pathways in comorbid medical disorders such as osteoporosis but also the interaction of these pathways in the disorder itself. The high burden of osteoporosis and fractures and the importance of primary prevention and harm minimisation make an independent investigation essential. This research will enable future researchers, clinicians and patients to better understand adverse events associated with bipolar disorder, and develop and evaluate monitoring strategies surrounding bone health in these individuals.

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**Ethics approval** Ethics approval has been granted from Barwon Health Research Ethics Committee (reference number 10/89).

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