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# Lithium use and bone health in women with bipolar disorder: A cross-sectional study

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## Abstract

**Introduction:** Several psychiatric disorders and medications used to treat them appear to be independently associated with skeletal deficits. As there is increasing evidence that lithium possesses skeletal protective properties, we aimed to investigate the association between lithium use and bone health in a group of women with bipolar disorder.

**Method:** Women with bipolar disorder ($n = 117$, 20+ years) were recruited from south-eastern Australia. Bipolar disorder was confirmed using a clinical interview (SCID-I/NP). Bone mineral density (BMD; g/cm$^2$) was measured at the spine, hip and total body using dual-energy x-ray absorptiometry and low bone mass determined by BMD T-score of $<-1.0$. Weight and height were measured, socioeconomic status (SES) determined and information on medication use and lifestyle factors self-reported. Linear and logistic regression were used to test associations between lithium and (i) BMD and (ii) low bone mass, respectively.

**Results:** Thirty-five (29.9%) women reported current lithium use. Lithium users and non-users differed in regard to SES and BMD; otherwise, groups were similar. After adjustments, mean BMD among lithium users was

5.1% greater at the spine (1.275 [95% CI 1.229–1.321] vs. 1.214 [1.183–1.244] g/cm$^2$, $p = 0.03$), 4.2% greater at the total hip (0.979 [0.942–1.016] vs. 0.938 [0.910–0.966] g/cm$^2$, $p = 0.03$) and 2.2% greater at the total body (1.176 [1.148–1.205] vs. 1.150 [1.129–1.171] g/cm$^2$, $p = 0.08$) compared to participants not receiving lithium. Lithium users were also less likely to have low bone mass (22.9% vs. 43.9%, $p = 0.031$). Associations persisted after adjustment for confounders.

**Conclusion:** These data suggest lithium is associated with greater BMD and reduced risk of low bone mass in women with bipolar disorder. Research into the underlying mechanisms is warranted.

**KEYWORDS**

bipolar disorder, bone, bone density, lithium, psychiatry

## 1 | INTRODUCTION

Bipolar disorder is a chronic psychiatric disorder associated with high levels of medical burden and premature aging.[1,2] Recent research suggests that patients with bipolar disorder are disproportionately affected by osteoporosis and have an increased risk of fracture.[3] Both the condition and the medications used to treat it, for example, antipsychotics and antidepressants, have been suggested to adversely impact bone health.[4] Preliminary evidence suggests that lithium might counterbalance some of these negative effects.[5]

Lithium is the gold standard treatment for bipolar disorder with demonstrated mood stabilizing effects.[6–8] Besides its effects on mood, lithium has many off-target properties.[9] The side effects of lithium, particularly those related to thyroid and kidney function, are well-documented and are the most likely reason for the underutilization of lithium treatment in recent years.[10] Less is known, however, about lithium's effects on other biological systems, including its potential benefits. These include its potential to reduce cardiovascular and all-cause mortality.[11,12] Accumulating data show that lithium may also present neuroprotective, osteoprotective and potentially anti-cancer properties, thus shifting the balance around its potential deleterious effects.[6–9]

One of the understudied potential benefits of lithium involves its effects on bone health. A recent study in Denmark showed that patients with bipolar disorder are at increased risk for osteoporosis, identified via hospital diagnoses and prescribed medications and found that those taking lithium had a lower risk of the condition when compared to users of other drugs and even the general population.[13] However, few studies have investigated the effects of lithium on bone mineral density (BMD), a more objective marker of bone health.[5,14]

In this study we aimed to determine lithium's potential effects on bone health in a sample of women with bipolar disorder enrolled in a large population-based study. We hypothesize that lithium use would be associated with higher BMD and reduced risk of low bone mass when compared to women with bipolar disorder not receiving lithium.

### Significant outcomes

- In this sample of 117 Australian women with bipolar disorder, lithium use was associated with greater bone mineral density at the spine (5.1% higher), hip (4.2%), and total body (2.2%) compared to women with bipolar disorder receiving other treatments.
- Women with bipolar disorder taking lithium were also less likely to have low bone mass compared to controls (22.9% vs. 42.7%).
- Given the vast evidence that bipolar disorder is associated with adverse effects on bone health, optimal management of bipolar disorder should involve screening and treatment of bone-related disorders.

### Limitations

- The cross-sectional study design precludes any causal interpretation.
- Although this is one of the largest samples of women with bipolar disorder to measure bone mineral density, the relatively small number of lithium users might have limited statistical power.
- The specific and homogeneous sample of women with bipolar disorder included in the study does not allow for results to be extrapolated to other populations.

## 2 | METHODS

### 2.1 | Participants

Women with a history of bipolar disorder ($n = 117$) were recruited from public and private healthcare settings located in the Barwon Statistical Division, south-eastern Australia. To be considered for inclusion in the study, participants were required to be aged 20 years or over, have the capacity to consent to participation and meet criteria for bipolar I, II or not otherwise specified (NOS). Diagnosis was confirmed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders Axis I Disorders, non-patient edition (SCID-I/NP). Further detail regarding sampling, recruitment and data collection has been published elsewhere.[15] The study was approved by the Barwon Health's Human Research Ethics Committee and written informed consent was obtained from all participants.

### 2.2 | Measures

#### 2.2.1 | Outcome

Areal bone mineral density (BMD; g/cm$^2$) was measured at the posteroanterior (PA) spine (L2–L4), total hip and total body using dual energy x-ray absorptiometry (Prodigy, GE Lunar, Madison, WI, USA). Trained personnel completed calibrations daily with equipment-specific phantoms. Low bone mass (osteopenia or osteoporosis) was determined by a BMD T-score of $<-1.0$ at the spine and/or hip.[16]

#### 2.2.2 | Exposures

Past and current medication use at the time of assessment was recorded from lists or containers brought to the study appointment. For this analysis, current use of lithium, other psychotropics (antidepressants, anticonvulsants, sedatives and/or hypnotics, movement disorder agents and antiemetics/antinauseants) and medications known to affect bone health positively (antiresorptives, hormone therapy, and calcium and vitamin D supplements) or negatively (oral glucocorticoids and thyroid hormones) were included.

Weight was measured to ±0.1 kg using electronic scales and standing height measured to ±0.01 m using a wall-mounted Harpenden stadiometer.

Information on lifestyle behaviors was obtained by self-report. Tobacco smoking (manufactured or "hand rolled" cigarette, cigar or pipe) was recognized if current. Mobility was measured on a 7-point scale ranging from "very active" to "bedfast"[17]; for this study, participants were classified as "active" if mobility was identified as "very active" or "active"; otherwise, participants were classified as "sedentary." Alcohol consumption and calcium intake were estimated from a validated food frequency questionnaire.[18]

The Index of Relative Socio-economic Advantage and Disadvantage (IRSAD) was used to determine area based socioeconomic status (SES). It is calculated from Socio-Economic Index For Areas (SEIFA) scores based on census data from the Australian Bureau of Statistics to determine the socioeconomic condition of individuals and households. Scores were grouped into quintiles with lower scores (Quintile 1) indicating greater disadvantage and higher scores indicating greater advantage (Quintile 5).[19]

### 2.3 | Statistical analyses

Differences between lithium users and non-users were determined using *t*-tests for parametric variables, Kruskal–Wallis for non-parametric continuous variables and Chi-square tests or Fisher's exact test for discrete variables. Linear regression models were developed to determine the association between lithium use and BMD (spine, hip, and total body) and logistic regression was used to determine the relationship between lithium use and low bone mass. Unadjusted, age- and weight-adjusted and best models, identified by backwards elimination of potential confounding variables, including age, weight, height, physical activity, smoking status, alcohol consumption, dietary calcium intake, SES, past use of lithium and current use of other psychotropics and medications known to affect bone (variables were retained in the model if $p < 0.05$) are presented. Interactions were tested in the best models. Statistical analyses were performed using Minitab (version 18, Minitab, State College, PA, USA).

## 3 | RESULTS

Thirty-five (35/117; 29.9%) women reported current lithium use. Median duration of use was 64 (35.3–144.5) months. Lithium users and non-users differed in regard to SES and BMD at the hip; otherwise, the groups were similar in age, weight, height, smoking status, activity levels, alcohol and calcium intake and BMD at the spine and total body (Table 1).

### 3.1 | Bone mineral density

Table 2 presents unadjusted, age- and weight-adjusted and best models showing associations between lithium use and hip, total body and spine BMD.

After adjustments, mean BMD among lithium users compared to non-users was 5.0% greater at the spine (1.275 [95% CI 1.229–1.321] vs. 1.214 [95% CI 1.183–1.244] g/cm$^2$, $p = 0.03$), 4.2% greater at the hip (0.979 [95% CI 0.942–1.016] vs. 0.938 [95% CI 0.910–0.966] g/cm$^2$, $p = 0.03$) and 2.2% greater at the total body (1.176 [95% CI 1.148–1.205] vs. 1.150 [95% CI 1.129–1.171] g/cm$^2$, $p = 0.08$). Smoking, physical activity, alcohol and calcium intake, SES, past lithium and other psychotropic medication use did not contribute to the models.

**TABLE 1** Characteristics of all participants, lithium users, and non-users.

| | | Lithium user | Lithium non-user | |
|---|---|---|---|---|
| | **All** | ***n* = 35** | ***n* = 82** | ***p*** |
| Age (year) | 48.1 (39.1–57.2) | 51.4 (41.5–58.3) | 46.5 (37.9–57.2) | 0.335 |
| Weight (kg) | 75.5 (65.3–90.2) | 77.3 (67.5–89.2) | 74.7 (65.1–90.7) | 0.479 |
| Height (m) | 1.64 ± 0.06 | 1.63 ± 0.07 | 1.64 ± 0.06 | 0.510 |
| Alcohol intake (g/d) | 3.1 (0.4–11.7) | 2.9 (0.4–17.1) | 5.1 (0.6–11.1) | 0.869 |
| Calcium intake (mg/day) | 833.0 (589.4–1066.0) | 715.7 (684.1–1005.9) | 901.9 (571.1–1207.3) | 0.052 |
| Smoking (current) | 29 (27.1%) | 11 (33.3%) | 18 (24.3%) | 0.333 |
| Mobility (active) | 77 (72.0%) | 24 (72.7%) | 53 (71.6%) | 0.906 |
| Socioeconomic status | | | | 0.032 |
| Quintile 1 (lowest) | 16 (13.9%) | 3 (8.8%) | 13 (16.1%) | |
| Quintile 2 | 18 (15.7%) | 8 (23.5%) | 10 (12.4%) | |
| Quintile 3 | 41 (35.7%) | 16 (47.1%) | 25 (30.9%) | |
| Quintile 4 | 26 (22.6%) | 7 (20.6%) | 19 (23.5%) | |
| Quintile 5 | 14 (12.2%) | 0 (0.0%) | 14 (17.3%) | |
| Medication use (current) | | | | |
| Antiresorptives | 1 (0.9%) | 0 (0.0%) | 1 (1.2%) | - |
| Glucocorticoids | 4 (3.4%) | 1 (2.9%) | 3 (3.7%) | - |
| Hormone therapy | 10 (8.6%) | 3 (8.6%) | 7 (8.5%) | 0.995 |
| Other psychotropics | 102 (87.2%) | 30 (85.7%) | 72 (87.8%) | 0.768 |
| Unadjusted BMD (g/cm$^2$) | | | | |
| Spine | 1.232 ± 0.144 | 1.277 ± 0.144 | 1.213 ± 0.140 | 0.030 |
| Total hip | 0.980 ± 0.116 | 1.012 ± 0.130 | 0.967 ± 0.107 | 0.079 |
| Total body | 1.181 ± 0.090 | 1.202 ± 0.088 | 1.171 ± 0.090 | 0.087 |
| Low bone mass (current) | 44 (37.6%) | 8 (22.9%) | 36 (43.9%) | 0.031 |

*Note*: Values are given as median (interquartile range), mean ± standard deviation or *n* (%).

**TABLE 2** Linear regression models showing associations between lithium use and BMD at the spine, hip, and total body.

| | **Model I: unadjusted** | | | **Model II: age- and weight-adjusted** | | | **Model III: best model**[a] | | |
|---|---|---|---|---|---|---|---|---|---|
| | ***B*** | **SE** | ***p*** | ***B*** | **SE** | ***p*** | ***B*** | **SE** | ***p*** |
| Spine | 0.064 | 0.029 | 0.027 | 0.063 | 0.028 | 0.026 | 0.061 | 0.027 | 0.028 |
| Hip | 0.045 | 0.023 | 0.056 | 0.042 | 0.019 | 0.029 | 0.041 | 0.019 | 0.031 |
| Total body | 0.031 | 0.018 | 0.087 | 0.027 | 0.015 | 0.072 | 0.026 | 0.015 | 0.077 |

*Note*: Values are given as beta coefficient, standard error, and *p* value.

[a]Best models, adjusted for: age, weight, and bone active medications.

### 3.2 | Low bone mass

Forty-four (44/117; 37.6%) women had low bone mass at the spine and/or hip. Lithium users were less likely to have low bone mass compared to non-users (22.9% vs. 43.9%, $p = 0.031$). This relationship was sustained following adjustment for age and weight (adj OR 0.32 [95% CI 0.12–0.86], $p = 0.023$). Smoking, physical activity, alcohol and calcium intake, SES, past lithium and other psychotropic use and medications known to affect bone did not contribute to the models.

## 4 | DISCUSSION

This cross-sectional study of 117 well-characterized women with a diagnosis of bipolar disorder found lithium users had greater spine, total hip and total body BMD compared to women with bipolar disorder not taking lithium. Lithium users also had a reduced risk of having low bone mass. Using a gold standard measurement of BMD and addressing several potential confounders, this study adds further evidence for lithium's potential role as a bone sparing agent in patients with bipolar disorder.

Our results align with epidemiological data linking lithium use with a decreased risk of osteoporosis and fracture.[13,20] A recent retrospective cohort study including 22,912 individuals with bipolar disorder from the Danish Psychiatric Research Central found that lithium use ($n = 8750$; 38.2% of bipolar patients) was associated with a 38% decreased risk of osteoporosis (Hazard Rate Ratio [HRR]: 0.62; 95% CI 0.53–0.72) compared to patients with bipolar disorder taking other drugs. Furthermore, a diagnosis of bipolar disorder was associated with an increased incidence of osteoporosis (8.7 [95% CI 8.28–9.14] per 1000 person-years) compared to 114,560 age- and sex-matched individuals without bipolar disorder (7.9 [95% CI 7.73–8.07] per 1000 person-years), resulting in a HRR of 1.14 (95% CI 1.08–1.20). Conversely, the incidence of osteoporosis in those with bipolar disorder treated with lithium was 5.98 (95% CI 5.23–6.83) per 1000 person years, an incidence rate lower than seen for those without bipolar disorder, suggesting a potential role for lithium as an osteoprotective drug even among the general population.[13]

Our study agrees with the only study that directly measured BMD in lithium users.[14] In this cross-sectional study of 75 lithium users, lithium use was associated with higher BMD at the spine (4.5% higher), femoral neck (5.3%), and trochanter (7.5%) compared to 75 matched controls. The study also assessed bone turnover and found lower serum levels of C-telopeptide, alkaline phosphatase and osteocalcin in those taking lithium, an indication of decreased bone remodeling. Parathyroid hormone (PTH) and urinary calcium did not differ significantly between groups. The authors concluded that lithium may preserve or increase BMD and that there is a lower bone turnover state in those taking lithium.[14]

A longitudinal study of 53 patients with bipolar disorder found that lithium significantly increased PTH levels at 6 months, an effect that was maintained throughout the 2 years of follow-up. However, the authors found that lithium significantly decreased calcium urinary excretion and reduced calcium net balance, opposite effects that were expected with high levels of PTH as seen in primary hyperparathyroidism. The unexpected finding led authors to postulate that "a counterregulatory factor" offset the hypercalcemic action of PTH by reducing bone resorption and that lithium was responsible.[21] This is an important mechanistic finding that deserves further exploration in light of recent research.

Lithium's influence on bone health is likely through a wide range of mechanisms, most described in detail in a recent review.[5] The most widely accepted mechanism suggests that lithium's effect is mediated by increased osteoblastic activity through its activation of Wnt beta/B-catenin via inhibition of glycogen synthase kinase 3B (GSK-3).[5,22,23] However, this mechanism fails to explain lithium's inhibition of osteoclastic differentiation, which seems to occur independently of this pathway.[5,23] Furthermore, the mechanism for lithium's widespread effects across biological systems remains elusive. One potential and underexplored mechanism involves lithium potential effects on a bone secreted hormone implicated in stress, brain function and metabolism, namely osteocalcin.[24] Osteocalcin has recently been implicated in multiple physiological processes in peripheral organs and the brain.[24] A recent and well-designed study implicated osteocalcin as the sole endocrine activator of the acute stress response.[25] The study demonstrated that mice (and humans) show a spike in osteocalcin levels within minutes of acute stress, an effect that is independent of adrenal activation (and consequent release of adrenaline and corticosteroids). The mechanisms involve a direct signal from the brain increasing glutamate uptake into osteoblasts that in turn release bioactive (uncarboxylated) osteocalcin into the circulation. Once released, osteocalcin suppresses the parasympathetic nervous system (at a central and peripheral level), allowing for unchecked sympathetic activation and enabling the acute stress response.[25] After careful consideration and taking into account a myriad of possible confounding factors, the authors suggest that the skeleton is the main mediator of the stress response, locally affecting peripheral tissues and brain function to enhance cognition, metabolism, and muscle function during periods of acute stress, an evolutionarily

conserved advantage that promoted survival in hostile environments.[25]

Although understudied, lithium's effects on osteocalcin signaling align with its wide range of effects on neuropsychiatric disorders and across biological systems.[9] Supporting this hypothesis, lithium use has been associated with decreased osteocalcin levels in bipolar patients compared to the general population while treatment-naive bipolar patients display higher levels of osteocalcin.[14,26] Osteocalcin seems to be elevated in depressed older adults and decreases significantly after successful treatment of depression.[27,28] We propose that lithium's effects on osteocalcin signaling cascades can explain some of lithium's effects on mood and other stress and age-related processes including lithium's neuroprotective, osteoprotective, anti-cancer and anti-aging properties.[5,29–33] Lithium has also been associated with weight gain, which theoretically should be associated with a positive effect on BMD. While lithium users appeared to have greater weight in this study, the difference between users and non-users was not significant. Further, adjusting statistical models for weight did not explain differences in BMD between lithium users and non-users.

Strengths of this study include the use of data from a comprehensively assessed group of women with bipolar disorder drawn from the population, which allowed us to account for several potential confounders, including physical activity levels and other lifestyle factors. The fact that we only include women with bipolar disorder, confirmed using a standardized diagnostic tool, eliminates the bias of confounding by indication. The use of a direct measurement of BMD is another strength. Limitations include its cross-sectional design, which precludes any causal interpretations, and the relatively small number of lithium users, even though this is still the largest sample of exclusively female participants with bipolar disorder to use a direct measure of BMD. The specificity of our sample hinders extrapolation of our results to other populations, including men and those without a history of bipolar disorder. To increase statistical power, we decided to group participants not taking lithium into one group but recognize that different classes of medication might differentially affect bone health. The absence of blood biomarkers to test the mechanistic hypothesis raised in this paper is another limitation.

In conclusion, this study provides further evidence for lithium's likely role in protecting bone health in women with bipolar disorder. We also hypothesize a new biological mechanism by which lithium effects on bone and osteocalcin signaling might be responsible for its effects on mood, cognition and other off target biological properties. Future studies should consider including markers of bone health and metabolism into assessments of mood disorders and treatment response. Also randomized clinical trials of lithium, largely neglected due to lithium's low commercial potential, are urgently needed to test this and other biological hypotheses.[9] These might unravel the likely underestimated role of bone metabolism in mental and overall health and provide much needed integrative therapeutic strategies for mood and somatic disorders. Lastly these findings, together with the documented benefits of lithium in suicide prevention and reduction of all-cause, cardiovascular and cancer mortality, reinforce its role as a unique first line therapy for bipolar disorder.

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## CONFLICT OF INTEREST STATEMENT

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## PEER REVIEW

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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