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Lithium and the risk of fractures in patients with bipolar disorder: A population-based cohort study

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ABSTRACT

Lithium is considered to be the most effective mood stabilizer for bipolar disorder. Evolving evidence suggested lithium can also regulate bone metabolism which may reduce the risk of fractures. While there are concerns about fractures for antipsychotics and mood stabilizing antiepileptics, very little is known about the overall risk of fractures associated with specific treatments. This study aimed to compare the risk of fractures in patients with bipolar disorder prescribed lithium, antipsychotics or mood stabilizing antiepileptics (valproate, lamotrigine, carbamazepine).

Among 40,697 patients with bipolar disorder from 1993 to 2019 identified from a primary care electronic health record database in the UK, 13,385 were new users of mood stabilizing agents (lithium:2339; non-lithium: 11,046). Lithium was associated with a lower risk of fractures compared with non-lithium treatments (HR 0.66, 95 % CI 0.44–0.98). The results were similar when comparing lithium with prolactin raising and sparing antipsychotics, and individual antiepileptics. Lithium use may lower fracture risk, a benefit that is particularly relevant for patients with serious mental illness who are more prone to falls due to their behaviors. Our findings could help inform better treatment decisions for bipolar disorder, and lithium's potential to prevent fractures should be considered for patients at high risk of fractures.

1. Introduction

People living with bipolar disorder are at higher risk for fractures, regardless of age, sex and comorbidities.(Chandrasekaran et al., 2019; Hsu et al., 2016) The higher risk of fractures could be attributed to two potential underlying mechanisms. The first mechanism is linked to the behavioral manifestation of bipolar disorder, including impulsive aggression, risk-taking behavior and violence, which may expose individuals to injuries and hence traumatic fractures.(Chandrasekaran et al., 2019; Chen et al., 2018; Pulay et al., 2008) A prior study found that individuals with bipolar disorder had twice the risk of traumatic fractures compared to those without bipolar disorder.(Hsu et al., 2016) Another mechanism is related to the pathogenesis of bipolar disorder, which affects bone metabolism. Evidence suggests that inflammation and immune dysregulation in the brain and periphery may contribute to the development of bipolar disorder.(Rege and Hodgkinson, 2013) The

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proinflammatory cytokine TNF-α may promote bone resorption, resulting in bone loss and poor bone health.(Kitaura et al., 2013; Munkholm et al., 2013; Schett, 2011) Furthermore, individuals with bipolar disorder often have unhealthy lifestyles due to suboptimal control of symptoms, which is a risk factor for osteoporosis and, subsequently, fractures.(Chandrasekaran et al., 2019) Thus, the occurrence of all-cause fractures may partially indicate the severity of bipolar disorder, and mood stabilizing treatment (lithium, antipsychotics and mood stabilizing antiepileptics) may help in preventing fractures.

Recent evidence suggests that lithium may have potential protective effects on fractures beyond mood stabilization. Lithium is a specific inhibitor of glycogen synthase kinase-3 beta, which enhances bone anabolism by osteoblasts, and may have potential osteoprotective effects.(Loiselle et al., 2013) This osteoprotective effect has been observed in animal and human studies, with increased bone mineral density (BMD) and decreased risk of fractures.(Clément-Lacroix et al., 2005; Liu et al., 2019; Loiselle et al., 2013) In contrast, several studies conducted in older adults, or patients with dementia have linked antipsychotics to increased risk of fractures.(Fraser et al., 2015; Graham et al., 2011; Lee et al., 2017; Wang et al., 2021) It has been unclear whether the increased risk could be due to factors other than exposure to antipsychotics and generalized to patients with bipolar disorder. In 2014, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK issued a warning that chronic use of antiepileptics may decrease BMD and hence lead to an elevated risk of fractures.(Medicines and Healthcare products Regulatory Agency, 2014) A previous meta-analysis reported a 1.9-fold increased risk of fractures associated with the use of antiepileptics.(Shen et al., 2014) However, specific associations between individual mood stabilizing antiepileptics and risk of fracture remain unclear.

Fracture is a significant concern among patients with mental illness, including bipolar disorder, as they may have less improvement in functionality and suffer more pain than people without mental illness. (Simske et al., 2019) The complications from fractures may lead to prolonged recovery, additional economic burden, and psychiatric comorbidities ranging from mild distress to mental disorders.(Foster et al., 2019; Klement et al., 2016) It is possible that these factors may contribute to worsening control of bipolar disorder. Therefore, it is crucial to investigate which mood stabilizing treatments may serve as safer alternatives for fracture prevention in patients with bipolar disorder.

This study aimed to compare the risk of fractures among patients with bipolar disorder treated with various mood stabilizing agents. We hypothesized that lithium may have a protective effect on fractures compared to other mood-stabilizing medications for bipolar disorder.

2. Method

2.1. Study design

This is a retrospective population-based cohort study, which was designed to emulate a clinical trial of a causal effect of bipolar disorder treatment on fractures using electronic medical records from a primary care database in the UK (Supplementary Table 1).(Hernán and Robins, 2016)

2.2. Data source

IQVIA Medical Research Data (IMRD-UK), formerly known as The Health Improvement Network (THIN) that is a proprietary database of Cegedim SA, is a nationally representative primary care database that contains anonymized data of more than 17 million patients from over 774 general practices scattered across the UK, representing around 6 % of UK population. The electronic health records collected from general practitioners (GPs) around the UK are for clinical management. IMRD-UK includes demographics, medical diagnoses made in both primary and secondary care, prescriptions, referrals, and lifestyle factors, such as weight and height, body mass index (BMI), smoking status and alcohol use. GPs enter medical diagnoses and symptoms using Read codes, which form a hierarchical coding system used to record clinical findings. The population in IMRD-UK is representative of the UK for demographics and major condition prevalence.(Blak et al., 2011) In the UK, patients, especially those with chronic illness and mental disorders, receive ongoing treatment from their GPs, so the prescriptions issued are well-defined in the cohort.(Health and Social Care Information Centre, 2012) The diagnoses of severe mental illness (including bipolar disorder) in primary care records have been validated.(Hardoon et al., 2013) This database has been used previously in pharmaco-epidemiological studies related to bipolar disorder.(Hardoon et al., 2013; Hayes et al., 2016b; Ng et al., 2021) This study protocol was approved by the Scientific Review Committee which was established to review research using the IMRD-UK database (Ref: 20SRC040).

2.3. Study cohort

The study population consisted of all individuals aged 18 years or above with a diagnosis of bipolar disorder who received at least one prescription for mood stabilizing agents (lithium, antipsychotics, or mood stabilizing antiepileptics [valproate, carbamazepine or lamotrigine]) between 1st January 1993 and 31st December 2019. Patients receiving a diagnosis of schizophrenia or schizoaffective disorder after their diagnoses of bipolar disorder were excluded. Diagnoses of bipolar disorder and schizophrenia were identified using Read codes. The date of the first prescription was defined as the index date. To identify new users of mood stabilizing agents, we excluded patients who received any aforementioned mood stabilizing agents within one year of patients' registration date with their associated general practice. Patients who had a diagnosis of bone tumors any time on or before the index date were excluded to reduce potential residual confounding on the outcome of interest.

2.4. Exposure

The exposure of interest was any mood stabilizing agents including lithium, antipsychotics, or mood stabilizing antiepileptics. For each prescription, treatment duration was calculated using the prescribed quantity and dosing frequency. Patients were assumed to have continuous treatment of the mood stabilizing agents if the subsequent prescription was issued within 3 months of the end of the prior prescription. To avoid the potential effect of the withdrawal syndrome of various mood stabilizing agents, a 3-month grace period was added to the end of the last prescription.(Tondo and Baldessarini, 2020) If the outcome of interest occurred during the grace period, it was considered to be associated with the drug treatment. To ensure the outcome of interest to be attributed to a specific drug class, patients who were prescribed more than one study drug class at the start of follow-up were excluded and those who received another study drug class during the follow-up time were censored.

2.5. Outcome

The outcome of interest was defined as any fractures, as identified using Read codes. The Read codes of fractures were referenced from a prior study to include newer fracture Read codes.(Davie et al., 2021)

2.6. Follow-up time

Patients were followed from the index date until the occurrence of fractures, death, transfer out of practice, switching to or receiving additional prescription(s) of another study drug class during the index treatment, discontinuation of treatment (>3 months between consecutive prescription refill) or end of the study period (31st December 2019), whichever was earlier.

2.7. Covariates

Patients' demographics, prior medical conditions, recent use of medications and lifestyle factors (BMI, smoking and alcohol use) were included as covariates. Details of covariates were summarized in Supplementary Table 2. Where there were multiple records for BMI, smoking status and alcohol use, the record closest to the index date was included. As GPs are less likely to record values that are within the normal range, in line with previous research,(Launders et al., 2022) patients with missing information on smoking, alcohol use or BMI were considered as non-smoker, non-drinker or normal, respectively.

2.8. Statistical analysis

Baseline characteristics were expressed as frequencies and percentages for categorical variables and mean and standard deviation (SD) for continuous variables. Cox proportional hazards regression model was applied to compare the rates of fractures among lithium and non-lithium groups in terms of hazard ratio (HR) with 95 % confidence intervals (CI). The time to occurrence of fractures for lithium and non-lithium groups was summarized by adjusted cumulative incidence curves.

To reduce any potential bias arising from the differences between the baseline covariates in different treatment groups, propensity score (PS) fine stratification weighting was used to control for confounding. Since the prevalence of lithium prescribing in the UK is low,(Ng et al., 2021) PS fine stratification weighting would provide greater precision and more confounding control compared to other PS-based methods.(Desai et al., 2017) The PS, a probability of receiving treatment based on the observed baseline covariates outlined, was estimated using logistic regression. PS was then used to create fine strata rather than directly calculating the weights. Weights for both the lithium and non-lithium groups (reference group) were calculated based on the total number of patients in each stratum. A total of 50 fine strata were created and the approach of average treatment effect among the treated population (ATT) was applied. After stratification, we applied weighting to ensure the baseline covariates were balanced. Standardized difference <0.1 was considered a negligible difference in covariates between treatment groups. To assess the effect of individual drug class, non-lithium group was stratified into antipsychotics (prolactin raising and prolactin sparing antipsychotics) and individual mood stabilizing antiepileptics in a separate analysis. The classification of prolactin raising and prolactin sparing antipsychotics is based on the review of literature.(Andrade, 2023; Huhn et al., 2019)

Several additional analyses were conducted to test for the robustness and validity of the results: 1) Males and females might have a different underlying risk of fractures and BMD, hence a sex-stratified analysis was conducted; 2) Patients with a history of fractures have a higher risk of subsequent fractures so patients were stratified by history of fractures to assess the effect of lithium against non-lithium on the recurrent fractures; 3) A sensitivity analysis was conducted by restricting to patients with at least two consecutive prescriptions of index treatment and each prescription lasts for more than 28 days; (Hayes et al., 2016b) 4) Additional sensitivity analysis using an intention-to-treat approach was conducted, whereby patients were not censored if they discontinued, switched, or received an additional prescription of another study drug class during the follow-up period; 5) To account for any potential residual confounding, E-value was calculated to estimate a minimum strength of association that an unmeasured confounder would need to have in order to nullify the observed association between the treatment groups and fractures, provided that all measured confounders were already adjusted (VanderWeele and Ding, 2017). The PS weights were re-calculated for all additional analyses.

All data manipulation and analyses were conducted by V.N. and M.L. independently for quality assurance using SAS (version 9.4) and R (version 3.5.3; R Core Team) respectively. A CI not overlapping 1.0 was considered statistically significant.

3. Results

3.1. Patient characteristics

During the study period, we identified 14,933 patients with bipolar disorder who newly received at least one prescription of any mood stabilizing agent. Following the exclusion criteria, a total of 13,385 patients were eligible for the analysis. Of these, 2339 received lithium as index treatment while 11,046 patients receiving antipsychotics and mood stabilizing antiepileptics were considered as non-lithium group (Fig. 1). The mean (SD) follow-up was 2.68 (4.00) years for the lithium group and 1.40 (2.31) years for the non-lithium group. The mean follow-up of the overall cohort was 1.62 (2.73) years. After applying PS fine stratification weighting, all baseline covariates were balanced with a standardized difference <0.1 (Table 1).

3.2. Risk of fractures

A total of 320 patients had fractures during follow-up (Supplementary Table 3). The adjusted cumulative incidence of fractures after treatment commencement was lower in lithium group than non-lithium group during the entire follow-up (Fig. 2). After PS fine stratification weighting, lithium was associated with a lower risk of fractures than non-lithium treatment (HR 0.66; 95 % CI 0.44 to 0.98) (Table 2). The corresponding E-value for the point estimate was 2.40 in an HR scale. Similar risks were also observed when comparing lithium with prolactin raising and sparing antipsychotics and individual mood stabilizing antiepileptics, respectively (Supplementary Tables 4).

The sex-stratified analysis showed imprecise lower risks of fractures for both males (HR 0.23; 95 % CI 0.08 to 0.64) and females (HR 0.76; 95 % CI 0.42 to 1.38). When excluding patients with a history of fractures, the result remained consistent with the main findings (HR 0.67; 95 % CI 0.44 to 1.01). The two sensitivity analyses that restricted to patients with at least two consecutive prescriptions of index treatment and each prescription lasts for more than 28 days (HR 0.68; 95 % CI 0.47 to 0.98) and using the intention-to-treat approach (HR 0.79; 95 % CI 0.68 to 0.92) also yielded similar findings.

4. Discussion

In this population-based cohort study, we found that patients with bipolar disorder who received lithium had a lower risk of all-cause fractures compared with those receiving non-lithium treatments. Similar effects are observed in head-to-head comparisons of lithium versus prolactin raising and sparing antipsychotics and individual mood stabilizing antiepileptics. The results of subgroup and sensitivity analyses remained robust with the main analysis.

Our findings are consistent with previous clinical studies reporting a decreased risk of fractures associated with lithium.(Vestergaard et al., 2005; Wilting et al., 2007) Two case-control studies conducted in Denmark and the UK compared the rate of fractures in patients who were ever treated with lithium with those who had never received lithium from the general population, while our study only included patients with bipolar disorder who prescribed mood stabilizing agents. (Vestergaard et al., 2005; Wilting et al., 2007) Despite the differences in the study cohort, healthcare systems and analytical methods used between studies, all three studies yielded similar conclusions, although the lower risk of fractures associated with lithium was more pronounced in our study.

Conversely, another cohort study in Taiwan reported no differences in the risk of fractures between lithium and non-lithium groups (including untreated patients) among patients with bipolar disorder. It is possible that patients without treatment may have less severe mood fluctuations and thus had a lower risk of fractures. However, in our study, we used patients who were treated with other mood stabilizing agents as the active comparator of lithium.(Su et al., 2017) Furthermore,

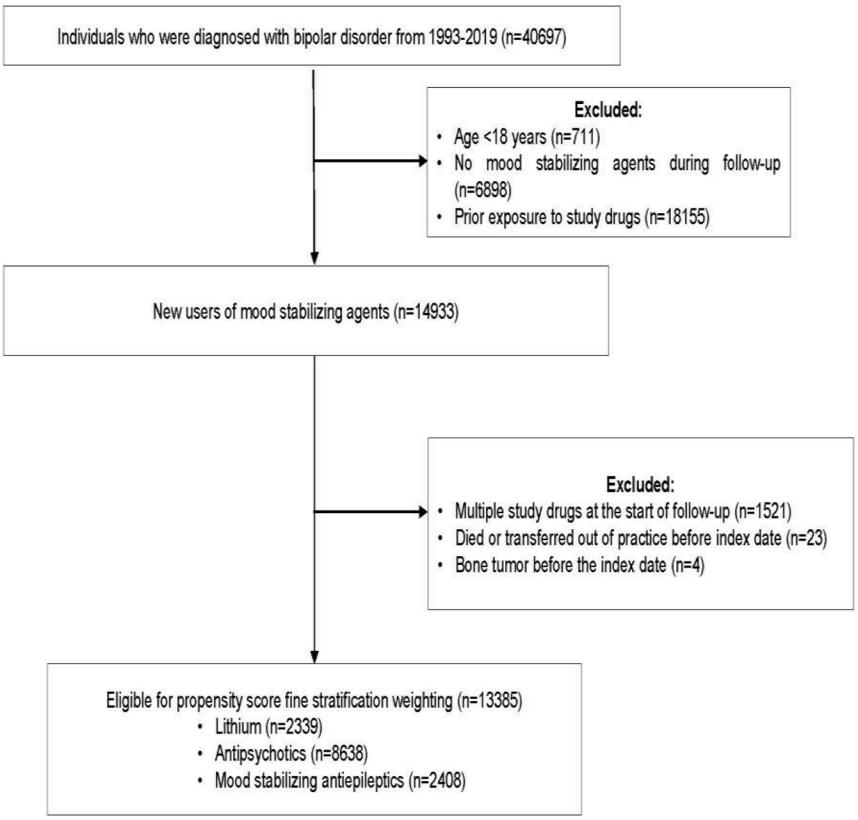

Fig. 1. Flow of selection of patients.

the previous study did not control for important risk factors of fractures, such as smoking, BMI, history of falls, which might bias the estimates. In contrast, our study addressed these confounding factors that were not fully accounted for in the previous study.

The findings that lithium was associated with a lower risk of fractures compared to other mood stabilizing agents among patients with bipolar disorder might be explained by several reasons. Firstly, lithium is considered the most effective mood stabilizer and superior to other antipsychotics or mood stabilizing antiepileptics in preventing relapse of mania and depressive episodes, reducing injuries, and impulsive aggression while such ability has not yet been identified in antipsychotics and mood stabilizing antiepileptics.(Hayes et al., 2016b; Miura et al., 2014) It is postulated that patients treated with lithium may be less likely to engage in risking-taking behaviors, hence resulting in fewer injuries and fractures.(Hayes et al., 2016b; Ng et al., 2022)

Secondly, the mechanism by which different classes of mood stabilizing agents have different effects on bone metabolism. Lithium has a specific role in enhancing bone anabolism and its potential beneficial effects on defective bones have also been previously reported, (Clément-Lacroix et al., 2005; Loiselle et al., 2013) however there was no significant difference in the risk between lithium and non-lithium use among patients with a history of fractures in our study, possibly due to limited sample size. Further studies with a larger sample will be warranted to investigate the effect of lithium on subsequent fractures. In contrast, antipsychotics would induce hyperprolactinemia via binding to dopamine D_2 receptors and antiepileptics reduce the intestinal calcium absorption and deactivate Vitamin D metabolism, all of which would ultimately result in increased bone loss and hence decreased BMD.(Holt and Peveler, 2011; Valsamis et al., 2006) Lastly, the adverse effects by antipsychotics (e.g. metabolic syndrome, and extrapyramidal effects) and antiepileptics (e.g. drowsiness, and motor incoordination) potentially increase the risks of falls and fractures.(Graham et al., 2011; Shen et al., 2014) Therefore, it is plausible that lithium may have a lower risk of fractures than antipsychotics and mood stabilizing antiepileptics and our findings further support this conclusion.

Fractures in patients with mental disorders often receive less attention from clinicians and researchers, despite the adverse impact on physical mobility, psychological complications, and economic burdens that can exacerbate the clinical progression of bipolar disorder. Therefore, prevention of fractures is highly important for management of bipolar disorder . Our finding that lithium was associated with a lower risk of fractures compared to non-lithium mood stabilizing agents is of clinical relevance for patients with bipolar disorder. The majority of patients with bipolar disorder have been treated with antipsychotics or mood stabilizing antiepileptics,(Ng et al., 2021) which may further increase the risk of fracture due to their potential mechanism of reduced BMD. Our study suggests that lithium could be a safer alternative to other mood stabilizing agents for preventing fractures, especially for those who are at high risk of fractures. More importantly, the problem of under-prescribing of lithium among patients with bipolar disorder aroused concerns in clinical practice and lithium's safety profile could be one of the reasons rendering lithium less preferable to antipsychotics or mood stabilizing antiepileptics.(Hayes et al., 2016a) Our findings contribute to the growing body of evidence of potential benefits associated with lithium beyond symptom control and help inform the benefit-risk assessment for clinicians' consideration when choosing between mood stabilizing agents for their patients.

There are notable strengths in this study. This study used a large and nationally representative electronic healthcare database in the UK. Secondly, PS fine stratification weighting used for confounding control has previously demonstrated better performance in terms of smaller relative bias and higher precision when the exposure is infrequent. (Desai et al., 2017) This was highly important in our study due to the low prescribing prevalence of lithium among patients with bipolar disorder .

There are some limitations to be acknowledged. IMRD-UK is a primary care database and therefore medications prescribed at the

Table 1
Baseline characteristics of study cohort.

Characteristics, No. (%)[a]	Before weighting			After weighting		
	Lithium	Non-lithium[b]	SMD	Lithium	Non-lithium[b]	SMD
Age, mean (SD)	49.1 (14.5)	44.2 (16.1)	0.314	49 (14.5)	48.8 (15.8)	0.013
Females	1393 (59.6)	6908 (62.5)	−0.061	1379 (59.6)	5939 (60.3)	−0.015
Comorbidities at baseline						
Cardiovascular diseases	82 (3.5)	454 (4.1)	−0.032	82 (3.5)	322 (3.3)	0.015
Prior stroke/ TIA	22 (0.9)	223 (2)	−0.089	21 (0.9)	123 (1.2)	−0.033
Hypertension	185 (7.9)	1161 (10.5)	−0.090	184 (8)	778 (7.9)	0.002
Diabetes mellitus	59 (2.5)	438 (4)	−0.082	58 (2.5)	248 (2.5)	0.0
Chronic kidney diseases	7 (0.3)	133 (1.2)	−0.105	7 (0.3)	32 (0.3)	−0.004
Chronic liver diseases	4 (0.2)	64 (0.6)	−0.067	4 (0.2)	15 (0.2)	0.005
Asthma	172 (7.4)	1532 (13.9)	−0.213	172 (7.4)	759 (7.7)	−0.010
COPD	23 (1)	200 (1.8)	−0.071	23 (1)	106 (1.1)	−0.008
Epilepsy	41 (1.8)	582 (5.3)	−0.192	41 (1.8)	195 (2)	−0.015
Rheumatoid arthritis and other inflammatory polyarthropathies	21 (0.9)	117 (1.1)	−0.016	21 (0.9)	111 (1.1)	−0.022
Osteoporosis	9 (0.4)	153 (1.4)	−0.107	9 (0.4)	39 (0.4)	−0.002
Thyroid diseases	117 (5)	471 (4.3)	0.035	115 (5)	511 (5.2)	−0.010
History of falls	70 (3)	553 (5)	−0.103	70 (3)	298 (3)	0.0
History of fractures	279 (11.9)	1952 (17.7)	−0.162	279 (12.1)	1212 (12.3)	−0.008
Medications at baseline						
Renin Angiotensin System Inhibitors (including ACEI and ARBs)	57 (2.4)	642 (5.8)	−0.170	56 (2.4)	239 (2.4)	0.0
β-blockers	131 (5.6)	754 (6.8)	−0.051	129 (5.6)	563 (5.7)	−0.006
Systemic glucocorticoids	28 (1.2)	276 (2.5)	−0.097	28 (1.2)	117 (1.2)	0.002
Proton pump inhibitors	94 (4)	948 (8.6)	−0.189	94 (4.1)	386 (3.9)	0.007
Sedatives (including opioids, anxiolytics, and hypnotics)	464 (19.8)	3415 (30.9)	−0.257	462 (20)	1998 (20.3)	−0.008
Antidepressants	1021 (43.7)	5896 (53.4)	−0.196	1014 (43.8)	4435 (45)	−0.024
Hormone replacement therapy	64 (2.7)	424 (3.8)	−0.062	64 (2.8)	271 (2.8)	0.001
Body mass index						
Underweight	34 (1.5)	376 (3.4)	−0.127	33 (1.4)	163 (1.7)	−0.019
Normal	1482 (63.4)	6019 (54.5)	0.181	1468 (63.4)	6178 (62.7)	0.015
Overweight	506 (21.6)	2653 (24)	−0.057	502 (21.7)	2034 (20.7)	0.026
Obese	317 (13.6)	1998 (18.1)	−0.125	311 (13.4)	1473 (15)	−0.044
Smoking status						
Current smoker	685 (29.3)	4006 (36.3)	−0.149	682 (29.5)	2871 (29.2)	0.007
Ex-smoker	193 (8.3)	1517 (13.7)	−0.176	192 (8.3)	798 (8.1)	0.007
Non-smoker	1461 (62.5)	5523 (50)	0.253	1440 (62.2)	6179 (62.7)	−0.011
Alcohol drinking status						
Current drinker	1170 (50)	6405 (58)	−0.160	1155 (49.9)	4818 (48.9)	0.020
Ex-drinker	47 (2)	319 (2.9)	−0.057	47 (2)	216 (2.2)	−0.011
Non-drinker	1122 (48)	4322 (39.1)	0.179	1112 (48.1)	4814 (48.9)	−0.017

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; SD, standard deviation; SMD, standardized mean difference; TIA, transient ischemic attack.

[a] Index years (1993–2019) and each care site were not reported in this table. The maximum SMD of index years and care sites is −0.022 and −0.054 respectively.

[b] Non-lithium group includes antipsychotics and mood stabilizing antiepileptics (i.e. valproate, carbamazepine, or lamotrigine).

secondary care are not recorded. However, GPs in the UK are responsible for providing ongoing treatment to patients and therefore the majority of the medications for chronic use are prescribed in primary care. In addition, this database is not linked to dispensing data from community pharmacies and hence whether the medications had been dispensed by the patients remained uncertain. Similar to other observational studies, patients' adherence to drug treatment is not recorded. Our findings remained robust after removing patients who received short-term treatment in the sensitivity analysis and does not affect our conclusion. Some of the baseline risk factors for fractures, such as BMD, exercise habits, dietary intake, are not available in the database. However, these attributes are not commonly considered to inform the choice of mood stabilizing agents for the management of bipolar disorder. The possibility of residual confounding remains although we accounted for confounding factors using PS methods. However, the calculated E-value suggested that our observed negative association with lithium compared with non-lithium treatments could only be explained by an unmeasured confounder that was associated with an HR of 2.40 each. This is much greater than common risk factors of fractures, such as other comorbidities, and concurrent use of medications.(Su et al., 2017) Therefore, it is unlikely that an additional unmeasured confounder of such a large magnitude would exist and change the overall conclusion.

In conclusion, our study found that lithium was associated with a lower risk of fractures compared to non-lithium treatments among patients with bipolar disorder. Similar effects were observed when comparing lithium to prolactin-raising and sparing antipsychotics and individual mood stabilizing antiepileptics. This association may be due to the benefits of lithium, including its osteoprotective effect and ability to reduce traumatic injuries, or the potential risk of fractures associated with non-lithium treatments. The reduction of fractures by lithium can improve patients' physical and psychological wellbeing and clinicians should consider this when prescribing mood stabilizing agents for their patients.

Data sharing statement

Data cannot be shared as the data custodian – IQVIA did not give permission due to the concerns of patient confidentiality and privacy. Further enquiries can be directed to the corresponding authors.

CRediT authorship contribution statement

Vanessa W.S. Ng: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Miriam T.Y. Leung:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Wallis C.Y. Lau:** Writing – review & editing, Methodology, Investigation. **Esther W. Chan:** Writing – review &

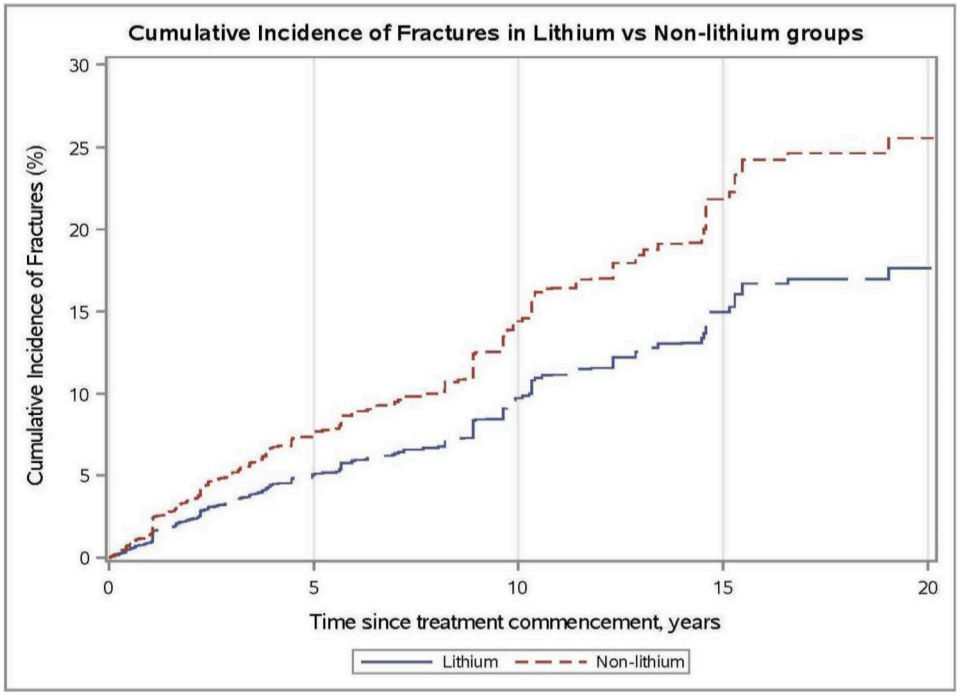

Fig. 2. Adjusted cumulative incidence of fractures in patients prescribed lithium, antipsychotics or mood stabilizing antiepileptics.

Table 2
Risk of fractures with lithium and non-lithium agents after propensity score fine stratification weighting.

Treatment	Lithium				Non-lithium[a]				Lithium VS Non-lithium	
	N	No. of events	Person-years	Adjusted incidence rate (per 100 person-years)	N	No. of events	Person-years	Adjusted incidence rate (per 100 person-years)	Adjusted hazard ratio (95 % CI)	P-value
Overall	2314	65	6196	1.05	9848	260	16,271	1.60	0.66 (0.44–0.98)	0.04
Stratified by sex										
Males	916	15	2532	0.59	2753	52	4306	1.21	0.23 (0.08–0.64)	0.005
Females	1376	50	3571	1.40	5280	142	8726	1.63	0.76 (0.42–1.38)	0.37
Stratified by history of fractures										
With history of fractures	235	13	445	2.92	657	24	881	2.72	5.92 (0.60–58.71)	0.13
Without history of fractures	2040	52	5636	0.92	7980	185	13,742	1.35	0.67 (0.44–1.01)	0.06
Sensitivity analyses										
Restricting to patients with at least two consecutive prescriptions of index treatment and each prescription lasts for more than 28 days	2174	63	6076	1.04	8578	229	14,957	1.53	0.68 (0.47–0.98)	0.04
Intention-to-treat approach	2314	348	31,356	1.11	9848	1771	126,132	1.40	0.79 (0.68–0.92)	0.003

Abbreviations: CI, confidence intervals; VS, versus.
[a] Non-lithium includes antipsychotics and mood stabilizing antiepileptics (i.e. valproate, carbamazepine, or lamotrigine).

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Declaration of competing interest

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Supplementary materials

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