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Lithium and the risk of severe COVID-19 infection: A retrospective population-based register study

Niklas Harry Nilsson [a,*], Marie Bendix [a,b], Louise Öhlund [c], Anna Gibbs [c], Micael Widerström [d], Ursula Werneke [c], Martin Maripuu [a]

[a] *Department of Clinical Sciences, Division of Psychiatry, Umeå University, Umeå, Sweden*
[b] *Department of Clinical Neuroscience, Center for Psychiatry Research & Stockholm Health Care Services, Stockholm County Council, Karolinska Institutet, Stockholm, Sweden*
[c] *Department of Clinical Sciences, Division of Psychiatry, Sunderby Research Unit, Umeå University, Umeå, Sweden*
[d] *Department of Clinical Microbiology, Umeå University, Umeå, Sweden*

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ABSTRACT

Objectives: Previous research has suggested antiviral properties for lithium, including potential effectiveness against COVID-19 in vitro. This study aimed to investigate the impact of lithium and other psychotropic drugs on the risks of mortality, hospitalization, and ICU admission due to COVID-19 among individuals with bipolar disorder. The primary objective was to assess whether lithium was beneficial in COVID-19-infection in a real-world population.
Methods: Retrospective register study using data from multiple Swedish patient registers, including 39,063 individuals in Sweden with bipolar disorder and prescribed mood stabilizers. Outcomes included COVID-19-associated death, hospitalization, and ICU admission between 11 March 2020 and 10 March 2021. Multivariate logistic regression adjusted for age, sex, and somatic comorbidities was conducted.
Results: Lithium were prescribed to 44.2 % of patients, either as mono- or combination therapy; other mood stabilizers were prescribed to 55.8 %. There were no significant associations between lithium and COVID-19-associated death, hospitalization, or ICU admission. Atypical antipsychotics were associated with increased odds ratios for COVID-19-associated death (OR 1.58 [95 % CI 1.01–2.47]), hospitalization (OR 1.80 [95 % CI 1.49–2.18]), and ICU admission (OR 2.25 [95 % CI 1.33–3.80]). Benzodiazepines were associated with a significant increase in COVID-19-associated death (OR 1.54 [95 % CI 1.01–2.35]) and hospitalization OR 1.26 [95 % CI 1.03–1.53]). In an ad hoc analysis, lithium monotherapy was, however, associated with reduced hospitalizations and ICU admissions.
Conclusions: Our findings weaken the hypothesis that lithium reduces the risk of severe events associated with COVID-19 infection in bipolar disorder.

1. Introduction

Lithium is widely used for treatment of bipolar disorder, known for its mood stabilizing effects [1]. In addition to its psychiatric benefits, lithium has been linked to various positive health outcomes, including reducing suicide risk, and lowering the incidences of dementia, osteoporosis, myocardial infarctions, and certain cancers [2–8]. Early in the COVID-19 pandemic, lithium was hypothesized to offer protection against the infection [9–13]. This hypothesis stemmed from studies indicating antiviral properties of lithium [14–16]. Notably, a Swedish study, using data before the pandemic, reported that lithium was associated with decreased risk of respiratory infections [17].

Preclinical research has suggested that lithium's immunomodulatory effects, mediated through the inhibition of glycogen synthase kinase-3 beta, could have therapeutic potential for coronavirus infections [13]. Furthermore, lithium has been shown to inhibit the replication of various viruses in vitro, including SARS-CoV-2, the virus causing COVID-19 [18]. Animal studies also suggest that lithium reduces disease

* Corresponding author.
E-mail addresses: niklas.nilsson@umu.se (N.H. Nilsson), marie.bendix@ki.se (M. Bendix), louise.ohlund@umu.se (L. Öhlund), anna.gibbs@umu.se (A. Gibbs), micael.widerstrom@umu.se (M. Widerström), ursula.werneke@umu.se (U. Werneke), martin.maripuu@umu.se (M. Maripuu).

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severity in COVID-19-infected hamsters [19]. A retrospective clinical study reported lower rates of COVID-19 infections among patients with therapeutic serum lithium concentrations compared to those treated with valproate [20].

Despite these potential benefits, lithium is not without risks. It can adversely affect renal, thyroid and parathyroid function, become toxic, and contribute to weight gain [21–23]. These risks may be exacerbated in individuals with COVID-19, since the infection can lead to gastrointestinal symptoms that can result in dehydration and acute kidney injury, increasing the risk of lithium toxicity [24,25].

While lithium is effective for many individuals with bipolar disorder, not all respond to it [26]. Other commonly used mood stabilizers include antiepileptics and antipsychotics [27]. These medications may also impact COVID-19 outcomes, for instance by affecting immune or respiratory function [28–30]. For instance, antipsychotics have been associated with increased risk of severe COVID-19 disease and mortality [31,32]. Their contribution to obesity, a known risk factor for severe COVID-19 infection, further compounds this risk [33,34]. Similarly, benzodiazepines, though not mood stabilizers but frequently prescribed for bipolar disorder [35], may exacerbate the risk of poor outcomes due to their potential for causing respiratory depression [28,36–38].

Individuals with severe mental disorders, including bipolar disorder, are at increased risk of adverse COVID-19 outcomes, such as hospitalization and death [39–45]. Although somatic comorbidities such as diabetes, cardiovascular disease, and pulmonary disease are more prevalent in this population, they do not fully explain the excess mortality observed [46–48]. The impact of psychiatric medications in influencing these outcomes remains underexplored. Therefore, investigating the potential benefits and risks of lithium and other psychotropic medications in the context of COVID-19-infection in this population is warranted.

This study aims to test the hypothesis that individuals with bipolar disorder prescribed lithium have a lower risk of severe COVID-19 compared to those treated with other mood stabilizers. To test this, we conducted a retrospective register study, examining the effects of lithium and other psychotropic medications on COVID-19-associated mortality, hospitalizations, and ICU admission in individuals with bipolar disorder.

1.1. Methods

This retrospective cohort study was based on data from multiple Swedish national registers. The register data was pseudonymized by the Swedish National Board of Health and Welfare and linked by the research team. The study was approved by the Swedish Ethical Review Authority (DNR 2020-02759).

1.2. Data sources

Individuals with bipolar disorder were identified from the Swedish National Patient Register [49]. Information regarding the cause-of-death, coded according to the International Classification of Disease 10th revision (ICD-10) [50], was retrieved from the Swedish Cause-of-Death Register [51]. Data regarding intensive care unit (ICU) admissions were retrieved from the Swedish Intensive Care Registry [52]. Medicine prescription data was retrieved from the Swedish Prescribed Drug Register [53]. This register contains information on all prescribed drugs dispensed at Swedish pharmacies, coded according to the Anatomical Therapeutic Chemical (ATC) Classification System [54].

1.3. Study population

The study population consisted of all persons (≥18 years by 1 January 2020) in Sweden with recurrent diagnoses of bipolar disorder/ single manic episodes (ICD-10 codes F30 and F31) on at least two separate occasions between 2015 and 2019. To reduce the number of mis- and overdiagnosed patients, at least two dispensed prescriptions of one or more mood-stabilizing drugs used in the long-term treatment of bipolar disorder were required for inclusion. Mood-stabilizing drugs were defined as lithium, valproate, lamotrigine, carbamazepine, and typical or atypical antipsychotics.

1.4. Variable definitions

1.4.1. Outcomes

There were three outcomes: COVID-19 associated death, hospitalization, and ICU admission during the first year of the pandemic, starting with the WHO declaration of COVID-19 as a pandemic on 11 March 2020, which coincided with Sweden's first confirmed COVID-19-associated death [55,56]. The time interval of one year was chosen to encompass both the first and second waves of COVID-19 in the winter of 2020/2021 and to limit the impact of COVID-19 vaccinations on the data analysis. Only approximately 8.8 % of the general population in Sweden had been vaccinated by 11 March 2021 [57].

The outcome of death associated with COVID-19 was defined as registration of COVID-19 (ICD-10 codes U07-U10) as an underlying or contributing cause of death. The outcome of hospitalization was defined as a discharge diagnosis registered with the above-mentioned ICD-10 codes in the Swedish National Patient Register. For the outcome of ICU admission, a COVID-19 discharge diagnosis registered in the Swedish Intensive Care Registry was used. It was possible for the same individual to be included in more than one outcome.

1.4.2. Exposures

The main exposure was mood-stabilizing drug therapy. Drugs were categorized by pharmacologic class: lithium, antiepileptics, and antipsychotics, the latter further divided into typical and atypical. Benzodiazepines were also analyzed since commonly used in the treatment of bipolar disorder and associated with respiratory depression [28,35,58]. The following ATC-codes were used; lithium N05AN01; antiepileptics N03AG01, N03AX01 and N03AX09; antipsychotics N05AA-AX excluding N05AN01, and benzodiazepines N05BA-CD. Patients were considered exposed if they had collected at least two prescriptions of the same drug on separate occasions between 1 January 2019 and 11 March 2020.

Somatic comorbidities were also examined: diabetes, hypertension, cardiovascular diseases, and chronic respiratory diseases. To identify pre-existing comorbidities, these were included if registered within a five-year interval before the outcomes, i.e., between 11 March 2015 and 11 March 2020. We included somatic comorbidities known to be associated with bipolar disorder and identified as risk factors for severe COVID-19 [47,59]. The somatic comorbidities were identified in two ways, via (a) ICD-10 codes and (b) via extrapolation from the ATC codes registered in the Swedish Prescribed Drug Register. Whereas the Swedish National Patient Register mainly covers secondary care, the Swedish Prescribed Drug Register also includes primary care. The following ICD-10 and ATC codes were used; diabetes ICD E10–14, ATC A10; hypertension ICD-10 I10.9, I11–13, I15. ATC C02, C03, C07AB02, C08CA, C09; cardiovascular disease ICD-10 I20–25, I48, I50, I61, I64.9, I69.1, I69.3, I69.4, I69.8, I70; and chronic respiratory diseases ICD-10 J40–47, J60–67, J68.4, J70.1, J70.3, J96.1, J96.8, E84.0.

1.5. Statistical analysis

Descriptive statistics were used to determine the prevalence of COVID-19 outcomes. Using IBM SPSS statistics for Windows, version 28 (IBM Corp., Armonk, NY, USA), multivariate logistic regression analysis was performed to generate adjusted odds ratios (ORs) with 95 % confidence intervals. Two multivariate regression models were used; one adjusting only for age and sex for each factor, and a second model fully adjusted for drug covariates, age, sex, and somatic comorbidities.

Additionally, a subgroup analysis was performed on individuals receiving lithium treatment. A multivariate regression model, adjusted for age, sex, and somatic comorbidities, was used to compare outcomes between those receiving lithium monotherapy and those receiving lithium in combination with other mood stabilizers.

Baseline characteristics were compared between individuals treated with lithium monotherapy or combination therapy and those treated with other mood stabilizers. Student's *t*-test was used to compare the means of continuous variables, such as age. The Chi-square test was applied to assess differences in categorical variables, including somatic comorbidities and medication use. Fisher's exact-test (two-sided) was used for comparisons involving categorical variables with small sample sizes.

2. Results

A total of 39,063 individuals with bipolar disorder who were treated with mood stabilizers were included in the study. Among them, 17,255 (44.2 %) were treated with lithium either alone or combination therapy, while 21,808 were treated with other mood stabilizers. The group of individuals with lithium treatment were older than those with other mood stabilizers (mean age 52 ± 17 years versus 47 ± 16 years, $p < 0.001$) and fewer were female (60.5 % vs 65.9 %, $p < 0.001$). Chronic pulmonary diseases were more common in those without lithium treatment (6.3 % vs 5.0 %, $p < 0.001$). 39.8 % of individuals treated with lithium had no other mood-stabilizing treatment. More individuals with lithium were treated with nitrazepam ($p < 0.001$) and more individuals treated with other mood stabilizers were treated with diazepam ($p = 0.034$); otherwise, there were no significant differences in treatment with benzodiazepines. (Table 1).

Table 1
Baseline characteristics. Individuals with bipolar disorder treated with lithium in either mono- or combination therapy versus individuals treated with other mood stabilizers. $N = 39{,}063$.

Characteristic	Lithium	Other mood stabilizers	*p*-value
Total, n	17,255	21,808	
Age (years), mean ± SD	52 ± 17	47 ± 16	<0.001[a]
Female, n (%)	10,441 (60.5)	14,369 (65.9)	<0.001[b]
Comorbidities*, n (%)	5613 (32.5)	6931 (31.8)	0.116[b]
Hypertension	4291 (24.9)	5395 (24.7)	0.768[b]
Cardiovascular disease	1198 (6.9)	1545 (7.1)	0.586[b]
Diabetes	1689 (9.8)	2072 (9.5)	0.339[b]
Chronic pulmonary disease	866 (5.0)	1373 (6.3)	<0.001[b]
Medication use**, n (%)			
Lithium	17,255 (100)	0 (0)	
Monotherapy	6870 (39.8)	0 (0)	
Antiepileptics	5013 (29.1)	15,295 (70.1)	<0.001[b]
Valproate	1332 (7.7)	3063 (14.0)	<0.001[b]
Carbamazepine	185 (1.1)	304 (1.4)	0.004[b]
Lamotrigine	3675 (21.3)	12,455 (57.1)	<0.001[b]
Typical antipsychotics	742 (4.3)	1000 (4.6)	0.175[b]
Chlorpromazine	0 (0.0)	2 (0.0)	0.507[c]
Fluphenazine	1 (0.0)	1 (0.0)	1[c]
Perphenazine	69 (0.4)	80 (0.4)	0.599[b]
Prochlorperazine	0 (0.0)	1 (0.0)	1[c]
Haloperidol	280 (1.6)	360 (1.7)	0.828[b]
Flupentixol	108 (0.6)	211 (1.0)	<0.001[b]
Chlorprothixene	99 (0.6)	131 (0.6)	0.730[b]
Zuclopenthixol	212 (1.2)	247 (1.1)	0.382[b]
Pimozide	1 (0.0)	2 (0.0)	1.00[c]
Atypical antipsychotics	7758 (45.0)	11,903 (54.6)	<0.001[b]
Melperone	14 (0.0)	20 (0.1)	0.725[b]
Ziprasidone	97 (0.6)	126 (0.6)	0.839[b]
Lurasidone	179 (1.0)	171 (0.8)	0.008[b]
Clozapine	157 (0.9)	152 (0.7)	0.018[b]
Olanzapine	3103 (18.0)	3398 (15.6)	<0.001[b]
Quetiapine	3871 (22.4)	6434 (29.5)	<0.001[b]
Sulpiride	0 (0.0)	1 (0.0)	1[c]
Amisulpride	4 (0.0)	7 (0.0)	0.765[c]
Risperidone	675 (3.9)	845 (3.9)	0.850[b]
Aripiprazole	1380 (8.0)	2595 (11.9)	<0.001[b]
Paliperidone	103 (0.6)	161 (0.7)	0.090[b]
Cariprazine	19 (0.1)	21 (0.1)	0.672[b]
Benzodiazepines	3823 (22.2)	4914 (22.5)	0.374[b]
Diazepam	1042 (6.0)	1432 (6.6)	0.034[b]
Oxazepam	2360 (13.7)	3046 (14.0)	0.410[b]
Lorazepam	124 (0.7)	131 (0.6)	0.151[b]
Clobazam	1 (0.0)	1 (0.0)	1[c]
Alprazolam	364 (2.1)	508 (2.3)	0.144[b]
Nitrazepam	491 (2.8)	426 (2.0)	<0.001[b]
Flunitrazepam	36 (0.2)	38 (0.2)	0.438[b]
Triazolam	5 (0.0)	4 (0.0)	0.521[c]
Midazolam	4 (0.0)	13 (0.1)	0.086[b]

* Comorbidities recorded between 11 March 2015 and 11 March 2020. Individuals could have more than one comorbidity.
** Minimum 2 dispensed prescriptions on separate occasions between 1 January 2019 and 11 March 2020. Individuals could have treatment with more than one mood stabilizing drug.
[a] Student's *t* test.
[b] Chi-square test.
[c] Fisher's exact-test (Two-sided).

2.1. Death associated with COVID-19

There were 97 deaths associated with COVID-19 among individuals receiving treatment with mood stabilizers for bipolar disorder. Lithium treatment was associated with decreased odds ratios of COVID-19-associated death when only adjusting for age and sex (OR 0.61 [95 % CI 0.40–0.91], $p = 0.017$). There was no association between lithium and COVID-19-associated death in the fully adjusted model (OR 0.82 [95 % CI 0.56–1.30], $p = 0.399$). Treatment with atypical antipsychotics was associated with increased odds ratios for COVID-19-associated death in the model adjusted for age and sex (OR 1.77 [95 % CI 1.17–2.69], $p = 0.007$) and in the fully adjusted model (OR 1.58 [95 % CI 1.01–2.47], $p = 0.046$). Equally, treatment with benzodiazepines were associated with increased odds ratios in the model adjusted for age and sex (OR 1.78 [95 % CI 1.18–2.70], $p = 0.006$) and in the fully adjusted model (OR 1.54 [95 % CI 1.01–2.35], $p = 0.046$). There were no significant associations for antiepileptics, neither when only adjusting for age and sex or when fully adjusting. (Table 2).

2.2. Hospitalizations associated with COVID-19

There were 474 hospitalizations associated with COVID-19 among individuals receiving treatment with mood stabilizers for bipolar disorder. Treatment with typical antipsychotics was associated with increased odds ratios of COVID-19-associated hospitalization in the model adjusted for sex and age (OR 2.25 [95 % CI 1.67–3.03], $p < 0.001$) and in the fully adjusted model (OR 2.02 [95 % CI 1.50–2.72], $p < 0.001$). Equally, treatment with atypical antipsychotics was associated with increased odds ratios in the model adjusting for sex and age (OR 1.80 [95 % CI 1.49–2.18], $p < 0.001$) and in the fully adjusted model (OR 1.70 [95 % CI 1.40–2.07], $p < 0.001$). Finally, treatment with benzodiazepines was also associated with increased odds ratios of COVID-19-associated hospitalization when adjusting for sex and age only (OR 1.52 [95 % CI 1.25–1.84], $p < 0.001$) and in the fully adjusted model (OR 1.26 [95 % CI 1.03–1.53], $p = 0.026$). For lithium and antiepileptics, there were no significant associations, neither in the model adjusted for sex and age or the fully adjusted model ($p > 0.05$). (Table 3).

2.3. ICU admissions associated with COVID-19

There were 65 ICU admissions associated with COVID-19. Treatment with typical or atypical antipsychotics was associated with increased odds ratios of COVID-19-associated ICU admission both in the model adjusted for sex and age (typical antipsychotics OR 2.80 [95 % CI

Table 2
Factors affecting the risk of COVID-19-related death between 11 March 2020 and 10 March 2021 among individuals with bipolar disorder receiving mood stabilizer treatment. $N = 97$ (39,063 included in the analysis).

	Adjusted for sex and age		Adjusted multivariate model	
	OR (95 % CI)	*p*-value	OR (95 % CI)	*p*-value
Lithium	0.61 (0.40–0.91)	0.017	0.82 (0.52–1.30)	0.399
Typical antipsychotics	1.97 (1.01–3.84)	0.047	1.83 (0.92–3.63)	0.084
Atypical antipsychotics	1.77 (1.17–2.69)	0.007	1.58 (1.01–2.47)	0.046
Antiepileptics	1.07 (0.69–1.64)	0.774	0.92 (0.57–1.47)	0.719
Benzodiazepines	1.78 (1.18–2.70)	0.006	1.54 (1.01–2.35)	0.046
Age	–	–	1.14 (1.11–1.16)	<0.001
Sex	–	–	0.67 (0.44–1.02)	0.065
Diabetes	1.47 (0.91–2.36)	0.115	1.13 (0.69–1.84)	0.627
Cardiovascular disease	2.02 (1.32–3.09)	0.001	1.60 (1.03–2.50)	0.038
Hypertension	1.97 (1.24–3.12)	0.004	1.58 (0.97–2.58)	0.067
Chronic lung disease	1.59 (0.90–2.84)	0.114	1.24 (0.69–2.24)	0.469

OR, odds ratio. Logistic regression analysis. Inclusion in drug category ≥2 dispensed prescriptions on separate occasions between 1 January 2019 and 11 March 2020. Individuals could have treatment with drugs in multiple categories. Somatic comorbidities recorded between 11 March 2015 and 11 March 2020. Individuals could have more than one comorbidity.

Table 3
Factors affecting the risk of COVID-19-related hospitalization between 11 March 2020 and 10 March 2021 among individuals with bipolar disorder receiving mood stabilizer treatment. $N = 474$ (39,063 included in the analysis).

	Adjusted for sex and age		Adjusted multivariate model	
	OR (95 % CI)	*p*-value	OR (95 % CI)	*p*-value
Lithium	0.87 (0.72–1.04)	0.122	1.11 (0.91–1.35)	0.316
Typical antipsychotics	2.25 (1.67–3.03)	<0.001	2.02 (1.49–2.72)	<0.001
Atypical antipsychotics	1.80 (1.49–2.18)	<0.001	1.70 (1.40–2.07)	<0.001
Antiepileptics	1.06 (0.88–1.28)	0.514	1.13 (0.93–1.38)	0.229
Benzodiazepines	1.52 (1.25–1.84)	<0.001	1.26 (1.03–1.53)	0.026
Age	–	–	1.03 (1.02–1.04)	<0.001
Sex	–	–	0.90 (0.75–1.09)	0.282
Diabetes	2.18 (1.76–2.71)	<0.001	1.65 (1.32–2.07)	<0.001
Cardiovascular disease	1.63 (1.27–2.09)	<0.001	1.16 (0.90–1.50)	0.254
Hypertension	2.12 (1.73–2.60)	<0.001	1.73 (1.39–2.15)	<0.001
Chronic lung disease	2.08 (1.59–2.71)	<0.001	1.63 (1.24–2.14)	<0.001

OR, odds ratio. Logistic regression analysis. Inclusion in drug category ≥2 dispensed prescriptions on separate occasions between 1 January 2019 and 11 March 2020. Individuals could have treatment with drugs in multiple categories. Somatic comorbidities recorded between 11 March 2015 and 11 March 2020. Individuals could have more than one comorbidity.

1.33–5.88], $p = 0.007$; atypical antipsychotics OR 2.25 [95 % CI 1.33–3.80], $p = 0.003$) and in the fully adjusted model (typical antipsychotics OR 2.49 [95 % CI 1.18–5.28], $p = 0.017$; atypical antipsychotics OR 2.22 [95 % CI 1.29–3.81], $p = 0.004$). For lithium, antiepileptics or benzodiazepines, there were no significant associations, neither in the model adjusted for sex and age or the fully adjusted model ($p > 0.05$). (Table 4).

2.4. Lithium monotherapy vs. lithium in combination with other mood stabilizers

In the total cohort, 17,255 individuals with bipolar disorder were treated with lithium. Of these, 6870 (39.8 %) received lithium monotherapy, while the remaining individuals were treated with lithium in combination with other mood stabilizers. Within this cohort, 43 deaths were associated with COVID-19. After adjusting for age, sex, and somatic comorbidities, no significant difference in COVID-19-related mortality was observed between individuals treated with lithium monotherapy and those receiving lithium in combination with other mood stabilizers.

Among the lithium-treated subgroup, there were 216 COVID-19-associated hospitalizations. Lithium monotherapy was associated with significantly lower odds of hospitalization (OR 0.58 [95 % CI 0.43–0.78], $p < 0.001$) after adjusting for age, sex, and somatic comorbidities.

Additionally, there were 24 ICU admissions associated with COVID-19 in this subgroup. After adjusting for age, sex, and somatic comorbidities, lithium monotherapy was associated with a significant reduction in the odds of ICU admission (OR 0.27 [95 % CI 0.09–0.79], $p = 0.017$) compared to those treated with lithium in combination with other mood stabilizers. (Table 5).

Table 4
Factors affecting the risk of COVID-19-related admission to an intensive care unit between 11 March 2020 and 10 March 2021 among individuals with bipolar disorder receiving mood stabilizer treatment. $N = 65$ (39,063 included in the analysis).

	Adjusted for sex and age		Adjusted multivariate model	
	OR (95 % CI)	*p*-value	OR (95 % CI)	*p*-value
Lithium	0.63 (0.38–1.05)	0.078	0.86 (0.50–1.46)	0.564
Typical antipsychotics	2.80 (1.33–5.88)	0.007	2.49 (1.18–5.28)	0.017
Atypical antipsychotics	2.25 (1.33–3.80)	0.003	2.22 (1.29–3.81)	0.004
Antiepileptics	1.46 (0.89–2.41)	0.138	1.45 (0.89–2.53)	0.129
Benzodiazepines	1.19 (0.68–2.09)	0.538	0.93 (0.53–1.64)	0.799
Age	–	–	1.01 (0.99–1.03)	0.134
Sex	–	–	0.48 (0.29–0.78)	0.004
Diabetes	3.02 (1.72–5.29)	<0.001	2.24 (1.25–3.99)	0.007
Cardiovascular disease	0.74 (0.30–1.78)	0.497	0.49 (0.20–1.18)	0.111
Hypertension	2.71 (1.54–4.77)	<0.001	2.25 (1.26–4.04)	0.006
Chronic lung disease	1.52 (0.65–3.56)	0.334	1.24 (1.24–2.92)	0.630

OR, odds ratio. Logistic regression analysis. Inclusion in drug category ≥2 dispensed prescriptions on separate occasions between 1 January 2019 and 11 March 2020. Individuals could have treatment with drugs in multiple categories. Somatic comorbidities recorded between 11 March 2015 and 11 March 2020. Individuals could have more than one comorbidity.

Table 5
Comparison of lithium monotherapy vs. lithium in combination with other mood stabilizers on the risk of COVID-19-related death, hospitalization and intensive care unit admission among individuals with bipolar disorder receiving lithium treatment between 11 March 2020 and 10 March 2021 (17,255 included in the analysis).

	Death ($n = 43$)		Hospitalization ($n = 216$)		ICU admission ($n = 24$)	
	OR (95 % CI)	*p*-value	OR (95 % CI)	*p*-value	OR (95 % CI)	*p*-value
Lithium monotherapy	0.71 (0.39–1.31)	0.277	0.58 (0.43–0.78)	<0.001	0.27 (0.09–0.79)	0.017
Age	1.15 (1.11–1.19)	<0.001	1.03 (1.02–1.04)	<0.001	1.02 (0.99–1.05)	0.194
Sex	0.66 (0.35–1.23)	0.189	0.77 (0.58–1.01)	0.058	0.31 (0.13–0.72)	0.007
Diabetes	1.38 (0.66–2.88)	0.398	1.29 (0.90–1.84)	0.162	2.37 (0.92–6.07)	0.074
Cardiovascular disease	1.55 (0.79–3.02)	0.201	1.20 (0.81–1.76)	0.366	0.45 (0.10–2.10)	0.310
Hypertension	1.70 (0.85–3.43)	0.136	1.76 (1.29–2.39)	<0.001	1.72 (0.68–4.32)	0.251
Chronic lung disease	1.48 (0.57–3.87)	0.423	2.00 (1.32–3.04)	0.001	2.39 (0.69–8.29)	0.170

OR, odds ratio. Logistic regression analysis. Other mood stabilizers defined as antiepileptics and/or antipsychotics. Ongoing treatment defined as ≥2 dispensed prescriptions on separate occasions between 1 January 2019 and 11 March 2020. Somatic comorbidities recorded between 11 March 2015 and 11 March 2020. Individuals could have more than one comorbidity.

3. Discussion

Contrary to what we expected from review of the available literature, our main results showed no significant associations between lithium treatment and COVID-19-related mortality, hospitalization, or ICU admission. However, in an ad hoc analysis, lithium monotherapy compared to lithium treatment combined with other mood stabilizers was associated with a lower risk of hospitalization and ICU admission. In the main analysis, the odds ratios of COVID-19-associated death were significantly lower with lithium treatment in the model adjusted for age and sex only. However, this association did not persist in the fully adjusted multivariate model accounting for somatic comorbidities and treatment with other mood stabilizers and benzodiazepines. Thus, our findings suggest that lithium treatment is likely to reduce the risk of severe events associated with COVID-19, particularly if combined with other mood-stabilizers. Additionally, we observed increased odds ratios of severe COVID-19 illness among individuals undergoing treatment with antipsychotics or benzodiazepines.

3.1. Comparison with other studies

To our knowledge, this is the first study to investigate the effects of lithium treatment on COVID-19-associated mortality, hospitalizations, and ICU admissions. Thus, the results need to be considered in the context of studies that investigated other aspects of associations between COVID-19 infection and lithium. In contrast to our results, previous research has mainly reported a protective effect of lithium on the risk of COVID-19 infection. A large retrospective study by De Picker et al. reported a reduced incidence of COVID-19 in patients with therapeutic serum lithium levels compared to those with subtherapeutic levels. Additionally, patients with therapeutic lithium levels had a lower incidence of COVID-19 compared to matched patients receiving valproate treatment [20]. Another recent study reported that lithium treatment reduced COVID-19 symptoms in infected hamsters and inhibited replication of SARS-COV-2 in vitro [19]. While an association between lithium treatment and COVID-19 mortality has not been explored in previous studies, there have been other approaches. A nationwide Japanese study investigated if naturally occurring lithium in drinking water affected COVID-19 mortality and found no association [60]. The levels of serum lithium were likely much lower than therapeutic levels which could potentially explain the discrepancy between the reports. In the study by De Picker et al., one possible reason that individuals who maintained therapeutic serum lithium levels had a lower risk of contracting COVID-19 may be due to their ability to follow the requirements for lithium treatment, such as frequent blood testing [61]. The patients' adherence to lithium treatment may also correlate with their ability to comply with the strict restrictions imposed during COVID-19 lockdowns in many countries, such as the USA where the study was conducted. This adherence could potentially result in lower incidences of COVID-19. The absence of a lockdown in Sweden during COVID-19 and the comparatively relaxed restrictions in contrast to other countries could have contributed to the discrepancy between these studies [62]. However, the overall COVID-19-associated mortality pattern among individuals with severe mental disorders in Sweden was comparable to mortality reported in other countries with more stringent COVID-19 policies [41,45,48].

3.2. Antipsychotics

Regarding other psychoactive medications in our study, antipsychotic treatment prior to COVID-19 infection was associated with increased odds ratios for mortality, hospitalization, and ICU admission. The results are in line with two meta-analyses that found a significant association between antipsychotics and COVID-19 mortality [31,32]. However, a recent extensive retrospective multicenter study involving more than 59,000 adult patients hospitalized with COVID-19 in France, found no significant association between antipsychotic use and 28-day all-cause mortality, except for typical antipsychotics and loxapine [63]. They attributed these associations to residual indication bias, explained by the fact that typical antipsychotics are preferentially prescribed to patients with dementia or delirium, which by themselves are associated with increased risks of mortality in COVID-19 [64,65]. In contrast, when analyzing factors affecting COVID-19-associated mortality in our study, the odds ratios for atypical antipsychotics were statistically significant whereas the odds ratios for typical antipsychotics were not. This could be due to the smaller number of dispensed drugs in the typical antipsychotics category. However, the odds ratios were similarly increased for both typical and atypical generation antipsychotics in regard to hospitalization and ICU admission associated with COVID-19. It is conceivable that individuals with bipolar disorder who are prescribed antipsychotic treatment may form a subgroup with a more severe illness than those who are not prescribed such medication. The observed results could potentially reflect the severity of the illness rather than being solely influenced by the medication itself.

In the case of antipsychotics, there are several unknown factors to consider that may have affected the results. It is common for drugs like Quetiapine and Olanzapine to be taken as required. Unfortunately, due to the nature of the available data set, it was not possible to definitively differentiate between standing daily orders and as-needed orders. Also, antipsychotic treatment is often associated with low adherence due to side effects such as weight gain and cognitive impairment [66]. It is possible that patients collected but did not take the prescribed antipsychotics. Ultimately, however, discontinuation of antipsychotic medications for individuals with bipolar disorder for fear of COVID-19 may be unfavorable since the risk for relapse increase [67]. Further comprehensive studies are required, specifically addressing potential confounding factors such as disease severity, obesity, and smoking, to ascertain the potential risks associated with antipsychotic medication. This is particularly important, as psychotic disorders are more strongly associated with COVID-19-related mortality compared to other severe mental disorders [39,45].

3.3. Benzodiazepines

Benzodiazepine treatment prior to COVID-19 infection was associated with a significant increase in COVID-19-associated death and hospitalization, but not ICU admission. Previous research is limited, and the results have been inconsistent. A South Korean study found that chronic use of benzodiazepines was associated with a higher risk of hospitalization among COVID-19 patients [38]. Their study did not establish any significant association between benzodiazepines and the risk of contracting SARS-CoV-2, severe outcomes, or mortality. A Spanish study examined the hospital prognosis of COVID-19, and reported no disparities in mortality, ICU admission, or risk of acute respiratory distress syndrome between those using and not using benzodiazepines [37]. In line with our findings, a large study in France reported that the use of benzodiazepines within hospital settings increased the risk of COVID-19-associated death [36].

3.4. Lithium monotherapy vs. lithium in combination with other mood stabilizers

In the subgroup analysis comparing individuals receiving lithium monotherapy versus those on lithium combined with other mood stabilizers; lithium monotherapy was associated with significantly lower odds of hospitalization and ICU admission due to COVID-19 after adjusting for age, sex, and somatic comorbidities. These results should be interpreted with caution, as this was an ad hoc analysis not included in the original study plan. Nevertheless, the findings are noteworthy. It is possible that lithium per se may exert a protective effect against COVID-19, an effect that could be masked or counteracted in individuals receiving mood stabilizer combination therapy. However, it is important to consider that the lithium monotherapy subgroup may have primarily consisted of lithium responders, and thus less affected by their bipolar disorder. Another possibility to consider is that the results could be related to the fact that most of the individuals in the combination therapy subgroup were treated with antipsychotics (>75 %), which aligns both with our main analysis and previous research [31,32]. Future research should focus on analyzing the outcomes of lithium in specific combinations with other mood stabilizers.

3.5. Strengths and limitations

Our study has several strengths. By including all individuals in Sweden who received mood stabilizer treatment for bipolar disorder, we minimized the potential for selection and healthy user bias, significantly enhancing statistical power. Additionally, the study takes into consideration potential confounding somatic comorbidities and utilized nationwide registers that are widely recognized for their high level of validation [49]. Another strength of the study was the decision to include individuals with at least two separate diagnoses of bipolar disorder within a five-year period prior to the study. Furthermore, individuals were required to have obtained at least two separate prescriptions for a mood-stabilizing drug, commonly used in the long-term treatment of bipolar disorder, during the year preceding to the study period. These criteria were designed to ensure a valid, active, and consistent diagnosis of bipolar disorder, thereby reducing the potential of misdiagnosis or overdiagnosis.

However, our study also has limitations. Due to limitation in data, it was not possible to differentiate between bipolar disorder type 1 and type 2. Furthermore, our study did not control for comorbid psychiatric diagnoses, which could have confounded the results. Specifically, adjustments were not made for cases where a diagnosis of bipolar disorder transitioned into schizoaffective disorder, potentially introducing bias into the findings as individuals with psychotic disorders have an increased risk of COVID-19-associated mortality [39]. Moreover, the study design prevented the calculation of hazard ratios. However, any potential bias stemming from this limitation is likely to be minimal as the duration of the study period was relatively short and the incidence of observed outcomes were low compared to the cohort size. Finally, we based our subgroups on the use of medication the year before the pandemic and we could not follow laboratory data such as serum lithium levels. Thus, we do not know for sure if patients were taking their prescribed drugs. Nor do we know if they changed medication during the study period. We addressed this issue by controlling for the percentage of patients collecting their prescription within 90 days before the event of death. Although the prescription intervals may be longer than 90 days, this is a standard length in Sweden. Prescriptions were collected within that time frame by 87 % in the lithium group, 96 % in the antiepileptic group, 75 % in the antipsychotic groups, and 55 % in the benzodiazepine group.

Beyond the scope of the present study, there may be additional unmeasured confounders that contribute to the results. It is important to acknowledge that risk factors such as overweight, smoking, and substance use, as well as socio-economic factors including employment, income, and education, are not consistently recorded in the registers [68–71]. Data regarding the specific SARS-COV-2 variants responsible for infection were also not available. Due to the limitations of the registers and the retrospective nature of the study, it was not possible to further analyze the impact of these factors. To minimize the influence of confounding factors, it is essential for future research to obtain more accurate data on potential confounders and medication usage.

The main objective of the study was to assess the impact of lithium on COVID-19 outcomes. To ensure comparability, we chose to only include individuals with bipolar disorder who were prescribed mood-stabilizing medication, such as lithium, along with antiepileptics and antipsychotics. This decision stemmed from a significant portion of individuals with bipolar disorder not having any prescriptions for mood-stabilizing medication, which could potentially introduce inconsistency in the study population. Benzodiazepines were included due to their widespread usage in treating bipolar disorder, and their association with negative effects on immune response and respiratory function [28,58]. Due to the limitations of the available registers, it was not possible to specifically verify whether the prescribed medications were intended for mood-stabilization purposes. Consequently, selective serotonin receptor inhibitors (SSRIs), which are primarily used to treat unipolar depression and are relatively contraindicated in bipolar disorder, were excluded in the process of ordering data [72,73]. Since then, it has been reported that SSRIs could potentially reduce the severity and improve the outcome in hospitalized patients with SARS-CoV-2 [74,75]. However, a recent nationwide study in Denmark, which considered more confounding factors than previous studies, instead found a significant increase in COVID-19 mortality in patients treated with SSRI [76].

During the final months of the period under study, Sweden initiated COVID-19 vaccinations [77]. While the current dataset did not incorporate vaccination data, we estimate from a press conference from The Public Health Agency of Sweden that 8.8 % of the overall population in Sweden had been vaccinated by the conclusion of the examined period [57]. Notably, a substantial portion of these vaccinated individuals were elderly residents in care homes and home care personnel [78]. Given this context, it is probable that the proportion of vaccinated individuals in our study population was lower. Despite the presumed low vaccination rate among our study participants at the end of the study period, the potential influence of vaccination on the outcomes cannot be dismissed.

4. Conclusion

In this retrospective population-based register study, lithium treatment overall in individuals with bipolar disorder was not associated with reduced COVID-19-associated mortality, hospitalization, or ICU admission during the first year of the pandemic in our main analysis. However, lithium monotherapy was associated with reduced hospitalizations and ICU admissions though this group may consist of healthier individuals compared to those receiving combination therapy. Our findings partly contradict previous research, and thereby weakening the hypothesis that lithium is beneficial for COVID-19. Ultimately, further studies are needed to definitively determine if there is an association between lithium treatment and the risk of severe COVID-19 infection.

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Authors contribution

NHN, MM, UW, LÖ, MB, and MW were responsible for conceptualization and study design. NHN and MM were responsible for the acquisition of data, performing formal and statistical analysis, and writing the original draft. UW, LÖ, MB, MW, and AG for editing and critically reviewing the manuscript. All authors have read and agreed to the published version of the manuscript.

CRediT authorship contribution statement

Niklas Harry Nilsson: Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Marie Bendix:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Louise Öhlund:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Anna Gibbs:** Writing – review & editing, Validation, Supervision, Methodology. **Micael Widerström:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Ursula Werneke:** Writing – review & editing, Validation, Supervision, Methodology, Funding acquisition, Conceptualization. **Martin Maripuu:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

NHN, MM, LÖ, MB, MW and AG declare no competing interests. UW has received lecture honoraria from Lundbeck and Janssen and has served/serves on scientific committees for Janssen and Teva receiving honoraria for these activities.

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