Lithium is thought to have antiviral properties. In vitro, lithium inhibits replication of several viruses, including coronavirus strains. In a national registry study using pre-pandemic data, lithium was associated with decreased risk of respiratory infections. As patients with mood disorders are at an increased risk of coronavirus disease 2019 (COVID-19) and of severe or fatal outcomes when infected, a protective effect of lithium against COVID-19 would be particularly welcome. However, no study to date has investigated the effect of lithium on COVID-19 incidence. This study used electronic health records (EHR) to compare the incidence of COVID-19 infections and positive polymerase chain reaction (PCR) tests for SARS-CoV-2 between 1 day and 6 months after the lithium level, and (c) with a recorded diagnosis of bipolar disorder.

To rule out the confounding effect of concurrent antidepressant use, we compared cohorts of individuals on lithium with versus without concurrent antidepressant use. For completeness, we also restricted cohorts to individuals without antidepressants, although this analysis was underpowered (see Supplementary Data 1). To assess the specificity of the association with COVID-19, we repeated the analysis for non-COVID respiratory infection. We used skin infection as a negative control.

More details on the data and analyses are provided in Supplementary Data 1.

### Results

A total of 14,008 individuals with a recorded therapeutic lithium level (mean level 0.741 (s.d. = 0.163) mmol/L) and 12,546 individuals with a recorded subtherapeutic lithium level (mean level 0.352 (s.d. = 0.141) mmol/L) were identified (see Supplementary Table 1 for baseline characteristics). In total, 11,791 individuals were selected from each cohort after matching. Adequate matching was achieved for all characteristics and all robustness analyses (Supplementary Tables 1–5). From 103,018 patients with previous or concurrent use of any antipsychotics (and clozapine specifically), and previous or concurrent use of any antidepressant (and fluvoxamine specifically). In the analysis comparing lithium with valproate, patients with epilepsy were excluded from both cohorts.

Kaplan–Meier analysis and the Cox proportional hazard model (with log-rank test) were used to calculate the cumulative incidence and hazard ratio (HR) for the primary outcome. The proportional hazard assumption was tested with the generalised Schoenfeld approach. Sensitivity of the findings to unmeasured confounders was quantified with the E-value. Statistical significance was set at two-tailed P-values <0.05.

We tested the robustness of the primary association by separately analysing COVID-19 diagnosis and positive PCR test as outcomes and by restricting cohorts to individuals: (a) with all recorded lithium levels within the cohort’s reference range during the 6-month follow-up, (b) who were not vaccinated before or within 6 months after the index lithium level, and (c) with a recorded diagnosis of bipolar disorder.

Association between serum lithium level and incidence of COVID-19 infection

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### Summary

An antiviral effect of lithium has been proposed, but never investigated for coronavirus disease 2019 (COVID-19). Using electronic health records of 26,554 patients with documented serum lithium levels during the pandemic, we show that the 6-month COVID-19 infection incidence was lower among matched patients with ‘therapeutic’ (0.50–1.00) versus ‘subtherapeutic’ (0.05–0.50) lithium levels (hazard ratio (HR) = 0.82, 95% CI 0.69–0.97, P = 0.017) and among patients with ‘therapeutic’ lithium levels versus matched patients using valproate (HR = 0.79, 95% CI 0.67–0.92, P = 0.0023). Lower rates of infection were observed for both new COVID-19 diagnoses and positive polymerase chain reaction tests, regardless of underlying psychiatric diagnosis and vaccination status.

### Keywords

COVID-19; lithium; valproate; bipolar disorder; psychopharmacology.

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documented valproate use during the pandemic, 13,346 were selected as a second control cohort after matching.

Therapeutic (versus subtherapeutic) lithium level was associated with a significantly lower risk of COVID-19 within the next 6 months (cumulative incidence 3.01%, 95% CI 2.66–3.39% vs. 3.72%, 95% CI 3.32–4.16%, HR = 0.82, 95% CI 0.69–0.97, P = 0.017, E-value = 1.74, P-value for proportionality 0.35; Fig. 1a).

The risk was also lower compared with patients prescribed valproate (cumulative incidence 2.94%, 95% CI 2.62–3.30% vs. 3.69%, 95% CI 3.33–4.10%, HR 0.79, 95% CI 0.67–0.92, P = 0.0023, E-value 1.86, P-value for proportionality 0.50). The association remained significant in all robustness analyses (Fig. 1b and Supplementary Figs. 1 and 2). We found no significant effect of concurrent antidepressant use on COVID-19 incidence (HR 1.17, 95% CI 0.85–1.62, P = 0.17; restricting cohorts to individuals without antidepressants resulted in a large 95% CI that included the primary HR = 0.96, 95% CI 0.68–1.35), and no significant effect of lithium on risks of other respiratory or skin infections (Supplementary Fig. 1).

**Discussion**

Therapeutic lithium levels were consistently associated with lower risks of both COVID-19 and positive PCR tests for SARS-CoV-2. The mechanisms underlying this observation remain to be determined. In vitro studies have suggested that lithium exerts its antiviral effect by inhibiting RNA replication.2 The weaker and non-significant association with other respiratory infections suggests some specificity of our finding to SARS-CoV-2. However, this might also result from lack of statistical power as only data from 2020 to 2021 were used (a significant association was observed in pre-pandemic data). Larger samples are also required to estimate the individual impact of lithium and antidepressants on COVID-19 incidence.

**Limitations**

Our findings, although robust, come with inherent limitations of EHR data (see Supplementary Data 1). Other sources of confounding might include differences in the nature and frequency of healthcare contacts during the pandemic, and differences between patients who can maintain adequate lithium levels versus those who cannot. However, any unmeasured confounders would need to associate with both the difference in lithium serum concentration and COVID-19 infection with a relative risk of 1.74-fold each (i.e. the E-value) to explain away the observed association, which seems unlikely. Furthermore, the use of lithium serum concentrations rather than prescriptions allowed us to reliably determine lithium exposure while avoiding confounding by indication. Finally, the lack of association with skin infection (used as a negative control), and the robustness of the finding in various scenarios suggest that no major confounders were missed in our analysis.

**Implications**

Although several psychopharmacological compounds have been claimed to exert protective or detrimental effects on COVID-19 outcomes (for example fluvoxamine appears to improve prognosis whereas clozapine might worsen it9), very few studies have investigated the effect of psychotropic medication against COVID-19 incidence10 – with evidence on the effects of lithium lacking altogether. The number of patients exposed to lithium at the time of COVID-19 infection in the current study was too low to evaluate infection outcomes in any robust way. However, a reduced infection incidence likely translates into reduced burden of COVID-19-associated complications.

In summary, our results provide the first real-world evidence that therapeutic lithium levels are consistently associated with lower risks of COVID-19. These findings shed more light on the antiviral effects of lithium. Although its tolerability profile excludes lithium from repurposing against COVID-19 in the general population, our
findings inform the risk–benefit balance of lithium prescription for psychiatric indications. Head-to-head comparisons with other psychopharmacological compounds are needed to provide definite clinical recommendations, but the observed protective effect of lithium might offset clinicians’ reluctance to prescribe lithium and monitor serum concentrations during the pandemic.

**Declaration of interest**

J.R.G. is a member of the BJPsych editorial board but did not take part in the review or decision-making process of this paper. The other authors declare no conflict of interests.

**References**