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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 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) vs. 'sub-therapeutic' (0.05-0.50) lithium levels (HR 0.82, 95% CI 0.69-0.97, $p=0.017$) and among matched patients with 'therapeutic' lithium levels vs. 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 PCR tests, regardless of underlying psychiatric diagnosis and vaccination status.

Keywords: COVID-19, lithium, valproate, bipolar disorder, epidemiology, psychopharmacology

28 **Introduction**

29 Lithium has been proposed to have antiviral properties¹. In vitro studies have indicated that lithium
30 inhibits replication of several viruses, including coronavirus strains^{1,2}. Evidence from human studies
31 however remained limited, until a Swedish national registry study based on pre-pandemic data
32 demonstrated that lithium was associated with a 28% decreased risk for respiratory infections³. Since
33 patients with mood disorders are at an increased risk of COVID-19 infection⁴ and of severe or fatal
34 outcomes when infected⁵, a protective effect of lithium against COVID-19 would be particularly
35 welcomed. However, no study to date has investigated the effect of lithium exposure on the risk of
36 COVID-19 infection. This study used electronic health records (EHR) to compare the relative
37 incidence of COVID-19 infections and positive PCR tests for SARS-CoV-2 among patients with high
38 versus low lithium serum concentrations and versus patients using valproate.

39 **Methods**

40 We used TriNetX Analytics, a federated EHR network with anonymised data from 81 million patients
41 (both insured and uninsured). Participating healthcare organisations include hospitals, primary care
42 and specialist providers. Data de-identification is attested to through a formal determination by a
43 qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule. This formal
44 determination supersedes TriNetX's waiver from the Western Institutional Review Board (IRB).
45 Further details about TriNetX are provided in the Supplement and have been presented previously⁶.
46 We followed STROBE reporting guidelines.

47 We compared all patients with a lithium level between 0.5 and 1 mmol/L (named 'therapeutic' for
48 convenience) recorded between January 19, 2020 and October 27, 2021 in their EHR versus a
49 matched cohort with a level between 0.05 and 0.5 mmol/L (named 'subtherapeutic' for convenience)
50 as primary analysis, and versus a matched cohort using valproate during the same period, as
51 secondary analysis. The primary outcome was defined as a composite of confirmed COVID-19

52 diagnosis (ICD-10 code U07.1) or positive PCR test for SARS-CoV-2 between 1 day and 6 months
53 after the lithium level was recorded.

54 Cohorts were propensity-score matched for each of 73 covariates consisting of: sociodemographic
55 factors and comorbidities representing risk for COVID-19 and for more severe COVID-19 illness
56 (e.g. obesity, hypertension, substance misuse), as per our previous studies⁶, specific mood disorder
57 diagnosis, personality disorder, previous or concurrent use of any antipsychotics (and clozapine
58 specifically), and previous or concurrent use of any antidepressant (and fluvoxamine specifically). In
59 the analysis comparing lithium to valproate, patients with epilepsy were excluded from both cohorts.

60 Kaplan-Meier analysis and the Cox proportional hazard model were used to calculate the cumulative
61 incidence and hazard ratio for the primary outcome. The null hypothesis that the HR equals 1 was
62 tested using a log-rank test. The proportional hazard assumption was tested with the generalised
63 Schoenfeld approach. The E-value was used to quantify sensitivity of the findings to unmeasured
64 confounders⁷. Statistical significance was set at two-sided p-values < 0.05.

65 We tested the robustness of the primary association by separately analysing COVID-19 diagnosis and
66 positive PCR test as outcomes and by restricting cohorts to individuals (1) with all recorded lithium
67 levels within the cohort's reference range during the 6-months follow-up, (2) who were not vaccinated
68 before or within 6 months after the index lithium level, and (3) with a recorded diagnosis of bipolar
69 disorder. To assess the specificity of the association of lithium with COVID-19 infection, we repeated
70 the analysis with non-COVID respiratory infection. We also used skin infection as a negative control
71 outcome.

72 More details on the covariate definition, statistical analysis, and secondary analyses are provided in
73 the supplement.

74

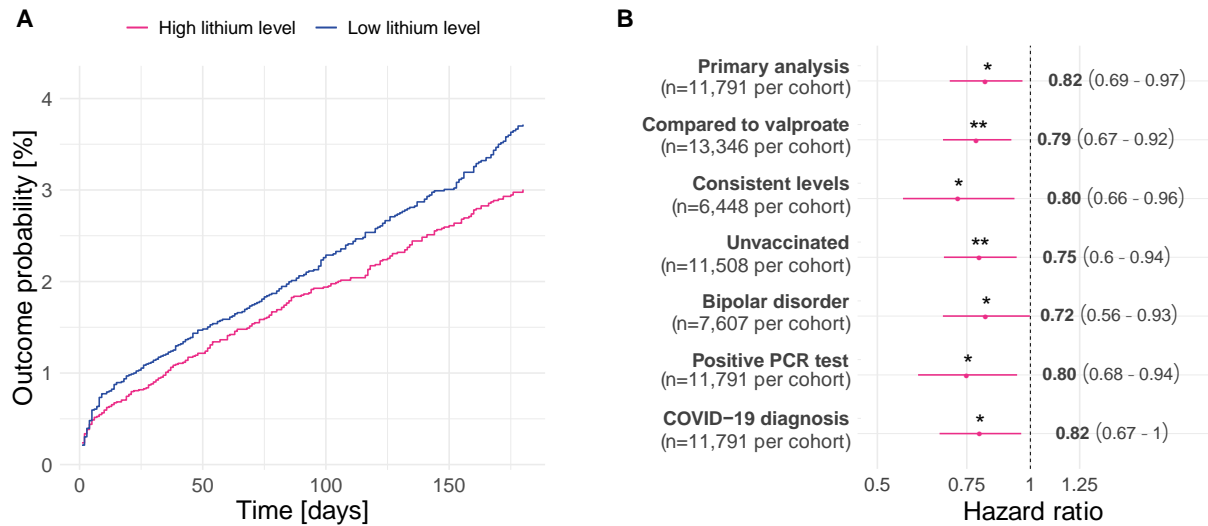
75

76 **Results**

77 A total of 14,008 individuals with a recorded lithium level between 0.5 and 1.0 mmol/L (mean [SD]
78 level 0.741 [0.163]) and 12,546 individuals with a recorded lithium level between 0.05 and 0.5
79 mmol/L (mean [SD] level 0.352 [0.141]) were identified (see Supplementary Table 1 for baseline
80 characteristics). 11,791 individuals were selected from each cohort after matching. Adequate
81 matching was achieved for all baseline characteristics and all robustness analyses (Supplementary
82 Tables 1-5). From 103,018 patients with documented valproate use during the pandemic, 13,346 were
83 selected as a second control cohort after 1-to-1 matching.

84 Therapeutic lithium level was associated with a significantly lower risk of COVID-19 infection within
85 the next six months compared to subtherapeutic lithium level (cumulative incidence 3.01%, 95% CI
86 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 -
87 value for test of proportionality 0.35; Figure 1A) and compared to valproate (cumulative incidence
88 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-
89 value 1.86, p -value for test of proportionality 0.50). The association remained significant in all
90 robustness analyses (Figure 1B and Supplementary Fig. 1-2). We found no significant protective
91 effect of lithium on rates of other respiratory or skin infections (Supplementary Fig. 1).

92



93

94 **Fig. 1** (A) Kaplan-Meier curves for the primary analysis showing the cumulative incidence of confirmed
 95 COVID-19 diagnoses or positive PCR test for SARS-CoV-2 after a therapeutic (red) vs. subtherapeutic (blue)
 96 lithium level in matched cohorts. The shaded areas around the curves [see pdf version of figure below] represent
 97 95% confidence intervals. (B) Hazard ratios for the comparison between matched cohorts in the secondary and
 98 robustness analyses. * $p < 0.05$, ** $p < 0.01$.

99 **Discussion**

100 Therapeutic lithium levels were consistently associated with lower risks of COVID-19 and positive
 101 PCR test for SARS-CoV-2. The mechanisms underlying this observation remain to be determined. In-
 102 vitro studies have suggested that lithium might exert its antiviral effect by inhibiting RNA
 103 replication². The weaker and non-significant association with other respiratory tract infections
 104 suggests some specificity of our finding to SARS-CoV-2. However, this might also be due to lack of
 105 statistical power resulting from our use of data from 2020-2021 only, as such an association has been
 106 shown in pre-pandemic data³.

107 Our findings, while robust, come with the inherent limitations of the EHR design (such as limited
 108 information about the accuracy or completeness of diagnoses; see Supplement and ref. 6 for
 109 discussion). In the context of the COVID-19 pandemic, other sources of unaccounted confounding
 110 might include differences in the nature and frequency of psychiatric healthcare contacts. However,

111 any unmeasured confounders would need to be associated with both the difference in lithium serum
112 concentration and COVID-19 infection with a relative risk of 1.74-fold each (i.e. the E-value) to
113 explain away the observed association, which seems unlikely. In addition, the use of lithium serum
114 concentrations rather than prescriptions allowed us to reliably determine lithium exposure, and to
115 investigate a dose-response relationship while avoiding confounding by indication. Furthermore, the
116 lack of association with skin infection (used as a negative control), and the robustness of the finding
117 in various scenarios also suggest that no obvious confounders were missed in our analysis.

118 While several psychopharmacological compounds have been claimed to exert either protective or
119 detrimental effects on COVID-19 *outcomes* (e.g. antidepressants and fluvoxamine in particular,
120 appear to improve COVID-19 prognosis⁸ whereas antipsychotics and clozapine in particular might
121 worsen it^{5,9}), very few studies have investigated the effect of psychotropic medication against the
122 *incidence* of COVID-19 – with evidence on the effects of lithium lacking altogether. The number of
123 patients exposed to lithium at the time of COVID-19 infection in the current study was too low to
124 evaluate infection outcomes in any robust way. However, the reduced number of new infections can
125 be reasonably expected to translate into a reduced burden of COVID-19-associated complications.

126 In summary, our results provide the first real-world evidence that therapeutic lithium levels are
127 consistently associated with lower risks of confirmed COVID-19 diagnosis and positive PCR test for
128 SARS-CoV-2. These findings shed more light on the antiviral effects of lithium. While its tolerability
129 profile might exclude lithium from repurposing against COVID-19 in the general population, our
130 findings can inform the risk-benefit balance of lithium prescription for psychiatric indications. Head-
131 to-head comparisons with other psychopharmacological compounds are needed to provide definite
132 clinical recommendations, but the observed protective effect of lithium might offset clinicians'
133 reluctance to prescribe lithium and monitor serum concentrations in the pandemic context.

134

135

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140 necessarily those of the UK National Health Service, NIHR, or the UK Department of Health.

141 **Declaration of interest**

142 The authors declare no conflict of interests.

143 **Author contributions**

144 LJDP, ML, JRG and MT formulated the research question. LJDP, PJH, and MT designed the study.
145 MT carried out the analyses. All authors contributed to interpretation of the findings. LJDP wrote the
146 first draft of the manuscript with input from MT. All authors revised the manuscript for content.

147 **Data Availability**

148 MT and PJH had full access to the data. The TriNetX system returned the results of these analyses as
149 csv files which were downloaded and archived. Data presented in this paper and the Appendix can be
150 freely accessed at [URL to be added on publication]. Additionally, TriNetX will grant access to
151 researchers if they have a specific concern (via the third-party agreement option).

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