

# Association between trace levels of lithium in drinking water and COVID-19-associated mortality

To the Editors

Lithium, widely used in treating bipolar disorder, also exhibits antiviral activity.<sup>1</sup> Lithium's antiviral effects may extend to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19).<sup>2</sup> Experimental data show that SARS-CoV-2 inhibition starts at very high lithium levels (>5 mEq/L).<sup>2</sup> This preliminary study investigates whether trace lithium, such as that in drinking water, may be associated with a low COVID-19 mortality.

In addition to the lithium data in drinking water from our recent study,<sup>3</sup> COVID-19-associated mortality data of all 47 prefectures in Japan as on August 22, 2020 were obtained from the Ministry of Health, Labour and Welfare in Japan. We calculated the mean lithium levels of all cities in the prefecture and the COVID-19-associated standardized mortality ratios (SMRs) of each prefecture. The population sizes across the 47 prefectures being very different and multiple regression analyses adjusted for each population size were performed to predict COVID-19 SMRs from the lithium levels and relevant factors of the prefectures, including the proportion of elderly people, the proportion of one-person households, the number of general hospitals per 100,000 people, and the number of deaths associated with diabetes mellitus, hypertension, and heart disease per 100,000 people.


The mean lithium level of the 47 prefectures was 2.37 µg/L (range: 0.4-11 µg/L). There was no significant association between the lithium levels and the COVID-19 SMRs in the crude model ( $\beta = -0.08$ ,  $p = 0.593$ ). After adjusting for the relevant factors using a stepwise method, the model could predict COVID-19 SMRs with statistical significance ( $F = 42.1$ ,  $p < 0.001$ ). However, the lithium level was not a significant contributor to the COVID-19 SMR ( $\beta = 0.073$ ,  $p = 0.367$ ). Among the relevant factors, only the proportion of elderly people ( $\beta = 0.629$ ,  $p < 0.001$ ) and the proportion of one-person households ( $\beta = -0.334$ ,  $p = 0.002$ ) were significant contributors.

Unlike the significant inverse association between the lithium levels in drinking water and suicide SMRs,<sup>3</sup> our findings suggest that trace lithium is not associated with a low mortality ratio in

COVID-19. The lack of significance might be due to the narrow range of lithium levels as we calculated the mean lithium levels of the cities of each prefecture to arrive at the lithium level of each prefecture. This was done because the number of COVID-19-associated deaths could not be obtained per city but per prefecture. A wider range of lithium levels might show a significant association. In any case, further studies are required to investigate the therapeutic effects of lithium for COVID-19.

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