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Lithium in drinking water and suicide prevention: The largest nationwide epidemiological study from Japan

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Abstract

Objectives: The aims of the present study thus were (a) to further investigate the association between lithium levels in drinking water and suicide rates by adjusting relevant factors using the so far largest available dataset in Japan, (b) to confirm sex differences, (c) to estimate the effects of long-term exposure to trace lithium, (d) to investigate the effects of drinking bottled instead of tap water, and (e) to exploratorily investigate which lithium levels may be associated with lower suicide rates.

Methods: Mean lithium levels in drinking water of all 808 cities and wards (ie, 785 cities of 46 prefectures and 23 wards of Tokyo) in Japan were examined in relation to mean suicide standardized mortality ratios (SMRs) during the 7 years from 2010 to 2016. Multiple regression analyses adjusted for the size of each population were used to investigate the association of lithium levels with suicide SMRs with adjustments for relevant factors.

Results: The adjusted model showed significant inverse associations of lithium levels with total and male SMRs, but not with female SMRs. Neither the proportion of residents who continued to live in the same city nor the consumption of bottled water changed the association between lithium levels and suicide SMRs. Finally, it was 30 μg/L or more that was associated with lower suicide SMRs.

Conclusions: The present findings reconfirm the inverse association between lithium levels in drinking water and suicide rates particularly in the male population.

KEYWORDS

drinking water, lithium, suicide prevention

1 | INTRODUCTION

An inverse association between lithium levels in drinking water and suicide rates was reported in 27 Texas counties in the United States in 1990.[1] In Japan, about 20 years later, we showed the same inverse association between lithium levels in drinking water and suicide rates in 18 municipalities of Oita Prefecture, where lithium levels in drinking water ranged from 0.7 to 59 μg/L,[2] in 274 municipalities of Kyushu island, where lithium levels ranged from 0 to 130 μg/L,[3] and in 153 cities of Kyushu island and Hokkaido island, where lithium levels ranged from 0.1 to 43μg/l.[4] All of these populations showed significant inverse associations between lithium levels in drinking water and suicide rates, particularly in male population.

Kapusta et al[5] showed that lithium levels in the drinking water of 99 Austrian districts ranged from 0 to 82.3 μg/L and that there was a significant inverse association with suicide rates, whereas Kabacs et al[6] showed no association between lithium levels in drinking water

and suicide rates in the 47 subdivisions of the East of England, where lithium levels in drinking water ranged from 0 to 21 μg/L. Thereafter, Blüml et al.[7] investigated Texas again and reported that the lithium levels in the drinking water of 226 Texas counties ranged from 2.8 to 219 μg/L, and that they were significantly and inversely associated with suicide rates. Giotakos et al[8] reported that lithium levels in the drinking water of 34 prefectures of Greece, ranging from 0.1 to 121 μg/L, were significantly and inversely associated with suicide rates. Sugawara et al[9] showed that lithium levels in the drinking water of 40 municipalities in Aomori Prefecture ranged from 0 to 12.9 μg/L, and that there was no significant association.

After 2015, Pompili et al[10] reported that lithium levels in the drinking water of 145 sites of Italy ranged from 0.11 to 60.8μg/l, and that lithium levels and suicide rates were not significantly related, except during the years from 1980 to 1989, particularly among women. Ando et al[11] reported that lithium levels in the drinking water of 24 public junior high schools in Kochi Prefecture in Japan ranged from 0.01 to 2.10 μg/l, and that they were not associated with suicidal ideation or self-harm in 3,040 students. Liaugaudaite et al[12] showed that lithium levels in the drinking water of nine cities in Lithuania ranged from 0.48 to 35.5 μg/L, and that there was a significant inverse association. Knudsen et al,[13] however, reported lithium levels in the drinking water of 275 municipalities in Denmark ranging from 0.6 to 30.7 μg/L and, surprisingly, suicide rates increasing with lithium levels. Palmer et al[14] showed that lithium levels in the drinking water of 15 counties in Alabama ranged from 0.4 to 32.9 μg/L, and that there was a significant inverse association with suicide rates, whereas Oliveira et al[15] showed that in 54 municipalities in Portugal, where lithium levels ranged from 0 to 191 μg/L, there was no association.

Although most of these past studies reported a significant inverse association between lithium levels in drinking water and suicide rates, recent studies (ie, published after 2015) showed inconsistent findings, such as inverse associations, direct associations, and no associations. Further studies are therefore required to draw reliable conclusions. Moreover, it seems necessary to reassess GENDER differences because of inconsistent findings,[16] to estimate the effects of long-term exposure to trace lithium,[17,18] and to investigate the effects of drinking bottled water instead of tap water because a significant proportion of people do not drink tap water. Finally, it is unknown which lithium levels may be associated with lower suicide rates.

In the present study, to our knowledge, the largest number of regions, 808 cities and wards all over Japan, were examined for an association between lithium levels in drinking water and suicide rates. The aims of this study were (a) to further investigate the association between lithium levels in drinking water and suicide rates, with adjustments for relevant factors, using the so far largest available dataset in Japan, (b) to confirm sex differences, (c) to estimate the effects of long-term exposure to trace lithium, (d) to investigate the effects of drinking bottled instead of tap water, and (e) to exploratorily investigate which lithium levels may be associated with lower suicide rates.

2 | METHODS

2.1 | Study population

Japan consists of four main islands, Hokkaido, Honshu, Shikoku, and Kyushu (listed from north to south). On March 31, 2010, Japan had 786 cities, and the largest city of Tokyo had 23 wards, each of which had a population as large as that of other cities. Therefore, we decided to investigate 808 regions, that is, all 785 cities and the 23 wards of Tokyo, for this study.

2.2 | Suicide data

Taking the large differences in gender and age distributions of individual city and ward populations into account, suicide standardized mortality ratios (SMRs) from 2010 to 2016 were calculated for each individual city and ward for each year and then averaged over the 7 years from 2010 to 2016. The SMR is an indirect method of assessing mortality rates, defined as the number of observed deaths in an individual city and ward population divided by the number of expected deaths, compared with the gender- and age-matched general population. We collected the available data on suicide from the Ministry of Health Labor and Welfare, and from the Statistics Bureau, Ministry of Internal Affairs and Communications.

2.3 | Measurement of lithium levels in drinking water

From 2010 to 2015, 988 tap water samples (usually from the main rail station or the municipal office) of each city and ward were analyzed by a third party using mass spectroscopy. This method can detect very small amounts of lithium; the minimal amount that can be measured is 0.1 parts per billion (0.1 μg/L). When the level was below 0.1 μg/L, we extrapolated the value to 0. If lithium levels in drinking water were measured at multiple times in the same city and ward, the mean value was calculated. Even when lithium levels were measured only once, we confirmed a very small fluctuation in levels, as the correlation coefficient between initial lithium levels and those remeasured after 1 year in the same places was 0.998.[2]

2.4 | Adjustment factors

We initially assessed the simple association between lithium levels in drinking water and suicide SMRs (total, male, and female) without any adjustments (crude model), but then further investigated the association by adjusting for proportions of elderly people, proportions of one-person households, proportions of people in primary industry employment, overall unemployment rates, annual marriage rates, annual mean temperatures, and annual total sunshine hours (adjusted model 1).Moreover, to estimate the effects of long-term

exposure to trace lithium, the mean proportion of residents who continued to live in the same city was calculated, as

Σ(i = 0 to 6)([population of the city on 201i March 31 − the number of residents who died and the number of residents moved out of the city from 201i April 1 to 201i + 1 March 31]/[population of the city at 201i March 31] × 100)/7.

and used as a further adjustment factor (adjusted model 2). Finally, to investigate the effects of drinking bottled instead of tap water, the house-hold consumption of bottled water in 47 cities that had a prefectural office and had data available was used as a further adjustment factor, but treated as a tentative factor, due to the low number of cities (adjusted tentative model).

The data on the proportions of elderly people, proportions of one-person households, proportions of people in primary industry employment, overall unemployment rates, and annual marriage rates were available for all 808 cities and wards, collected from the Statistics Bureau, Ministry of Internal Affairs and Communications, but only for the years 2010 and 2015, as the national census is performed every 5 years in Japan. Data relating to annual mean temperatures and annual total sunshine hours were partially available for 411 and 398 cities, respectively, from the Japan Meteorological Agency. The mean of the annual mean temperatures and annual total sunshine hours in 2010 and 2015 corresponding to the census was thus calculated for each individual city. For the cities where data were not available, we assumed the obtained data to roughly represent the neighboring cities as well, and the data were thus extrapolated to these cities, following a method described previously.[3]

2.5 | Statistical analysis

Due to great differences in population size across the 808 cities and wards, multiple regression analyses adjusted for the size of each population were used to predict suicide SMRs (total, male, and female) from lithium levels in drinking water and the above adjustment factors. Finally, we categorized the lithium levels into four groups (that is, 0 to less than 10 μg/L, 10 to less than 20 μg/L, 20 to less than 30 μg/L, 30 μg/L or more) to exploratorily investigate which lithium levels may be associated with the lower suicide SMRs.

This study was approved by the ethics committee of Oita University Faculty of Medicine, Oita, Japan.

3 | RESULTS

3.1 | Suicide data

The mean total, male, and female suicide SMRs for the years 2010 to 2016 were 103.3 (SD = 19.7; range, 55.1-245.8), 105.2 (SD = 22.9; range, 25.5-211.2), and 100.6 (SD = 26.6; range, 35.4-319.1) respectively.

3.2 | Lithium levels in drinking water

The mean lithium level in drinking water was 2.39μg/L (SD = 4.0; range, 0-43.0). Figure 1 is a map of Japan showing the city centers and distribution of lithium levels.

3.3 | Adjustment factors

The mean total, male, and female proportions of elderly people of the 808 cities and wards were 27.2% (SD = 5.3; range, 13.8-46.2), 24.0% (SD = 4.5; range, 13.0-40.4), and 30.1% (SD = 6.0; range, 14.6-51.3). The mean proportion of one-person households was 28.4% (SD = 7.2; range, 14.4-63.7),the mean proportion of people in primary industry employment was 5.9% (SD = 5.8; range, 0-31.4), the mean overall unemployment rate was 5.4% (SD = 1.3; range, 2.4-12.8), the mean total annual marriage rate was 4.7% (SD = 1.1; range, 2.5-11.7), the mean annual temperature was 15.1°C (SD = 2.4; range, 6.6-24.8), and the mean annual total sunshine was 1874.6h (SD = 192.4; range, 1187.1-2289.9). In addition, the mean proportion of residents who continued to live in the 808 cities and wards was 95.3% (SD = 1.1; range, 88.4-96.9), and the mean household consumption of bottled water of the 47 cities with available data was 2373.9 Japanese Yen (SD = 657.3; range, 1122.5-3960.0).

3.4 | Association between suicide SMRs and lithium levels

As shown in Tables 1-3, at the level of the crude model, there was no significant association between lithium levels and suicide SMRs in total, male, or female populations. After adjustments for relevant factors (adjusted model 1), however, total and male suicide SMRs, but not female SMRs, were significantly and inversely associated with lithium levels.

After further adjustments using the mean proportion of residents who continued to live in the same city (adjusted model 2), the significant inverse association between lithium levels and total suicide SMRs remained almost unchanged (β = −0.085 to −0.086, P = .008 to 0.008).

Limited to the 47 cities that had a prefectural office and provided data on the consumption of bottled water (adjusted tentative model), the inverse association between lithium levels and total suicide SMRs was not significant in the crude model (β = −0.077, P = .607), in the adjusted model 1 (β = −0.240, P = .076), in the adjusted model 2 (β = −0.243, P = .083), or in the adjusted tentative model that included the consumption of bottled water as a factor(β = −0.243, P = .090).

Exploratorily, we depicted the figures showing the association between lithium levels and suicide SMRs in total, male, and female populations (Figures 2-4). As shown in the figures, it appears 30 μg/L or more that was associated with lower suicide SMRs less than 100 (ie, a mean of suicide SMR all over Japan). Although these Figures 1-3

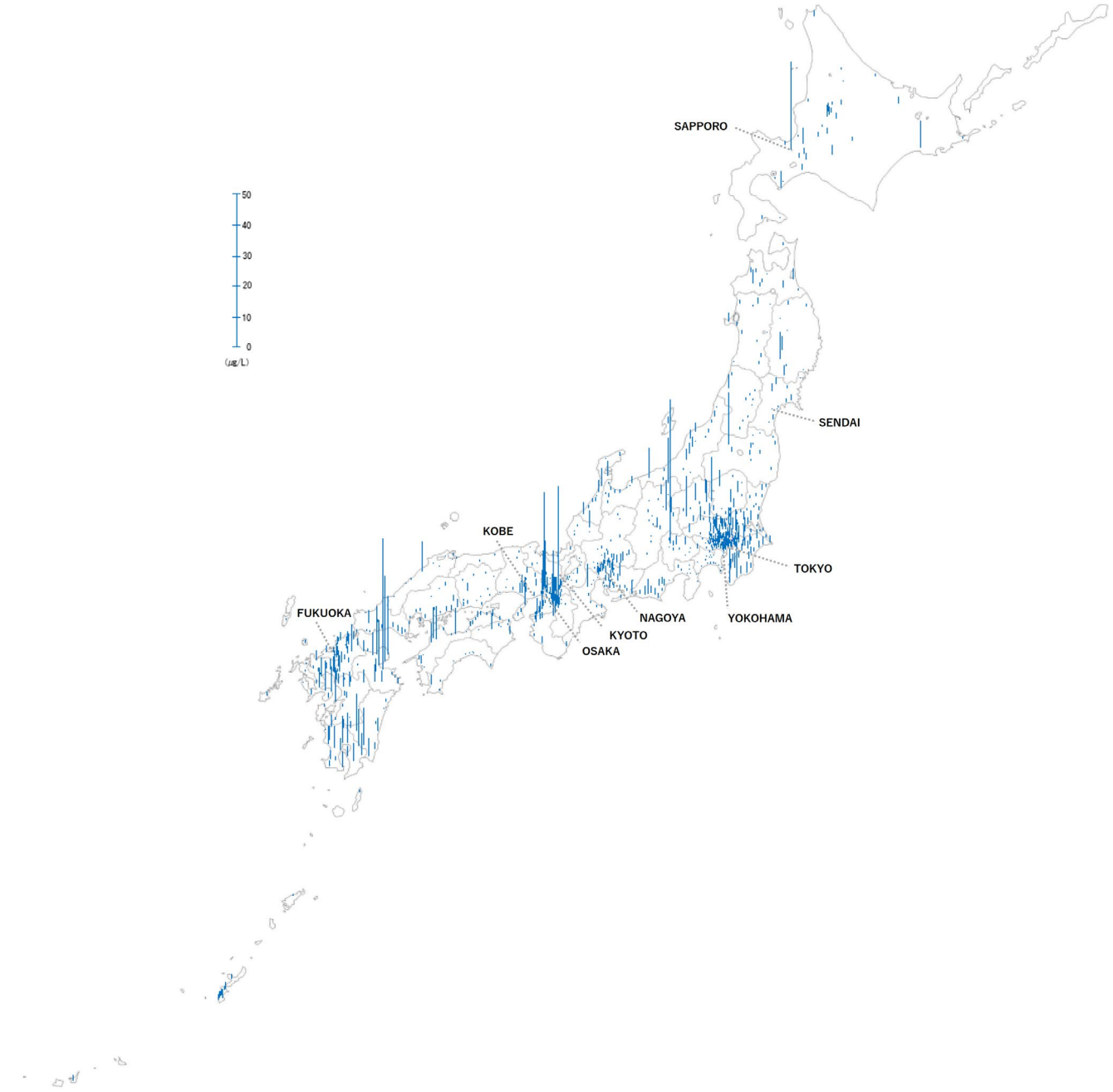

FIGURE 1 A map of Japan showing the city centers and distribution of lithium levels in blue

were not adjusted using relevant factors (the crude model), tentatively, one-way analyses of variance were performed, showing the significant difference of suicide SMRs along with the categorized lithium levels in total populations (F = 3.9, *P* = .009; suicide SMR = 103at lithium levels of 0 to less than 10μg/L, 115 at lithium levels of 10 to less than 20μg/L, 118 at lithium levels of 20 to less than 30μg/L, 87 at lithium levels of 30 μg/L or more)and male populations (F = 4.4, *P* = .004; suicide SMR = 105 at lithium levels of 0 to less than 10μg/L, 120 at lithium levels of 10 to less than 20μg/L, 123 at lithium levels of 20 to less than 30μg/L, 86 at lithium levels of 30 μg/L or more), but not in female populations (F = 0.5, *P* = .67; suicide SMR = 100at lithium levels of 0 to less than 10μg/L, 106 at lithium levels of 10 to less than 20μg/L, 106 at lithium levels of 20 to less than 30μg/L, 90 at lithium levels of 30 μg/L or more).

There was no multicollinearity in any of the multiple regression analyses.

4 | DISCUSSION

Although our crude, unadjusted model showed no significant association between lithium levels and suicide SMRs in total, male, or

TABLE 1 Association between lithium levels and total suicide SMRs

Model	β	*P*	adjusted R^2
Crude model			
Lithium levels	−0.024	.498	0
Adjusted model 1			
Lithium levels	−0.085	.008	0.232
Proportions of elderly people	0.267	.000	
Proportion of one-person households	−0.014	.784	
Proportion of people primary industry employment	0.282	.000	
Overall unemployment rate	0.247	.000	
Annual marriage rate	0.277	.000	
Annual temperature	−0.063	.078	
Annual total sunshine	−0.078	.033	

Note: Multiple regression analyses predicting total suicide SMRs revealed that at the level of the crude model, there was no significant association between lithium levels and suicide SMRs. After adjustments (adjusted model 1), however, total suicide SMRs were significantly and inversely associated with lithium levels.

TABLE 2 Association between lithium levels and male suicide SMRs

Model	β	*P*	adjusted R^2
Crude model			
lithium levels	0.017	.621	0
Adjusted model 1			
lithium levels	−0.061	.038	0.357
Proportions of elderly people	0.372	.000	
Proportion of one-person households	−0.002	.962	
Proportion of people in primary industry employment	0.372	.000	
Overall unemployment rate	0.291	.000	
Annual marriage rate	0.19	.001	
Annual temperature	−0.196	0	
Annual total sunshine	0.205	0	

Note: Multiple regression analyses predicting male suicide SMRs revealed that at the level of the crude model, there was no significant association between lithium levels and suicide SMRs. After adjustments (adjusted model 1), however, male suicide SMRs were significantly and inversely associated with lithium levels.

TABLE 3 Association between lithium levels and female suicide SMRs

Model	β	*P*	adjusted R^2
Crude model			
Lithium levels	−0.056	.11	0.002
Adjusted model 1			
Lithium levels	−0.054	.136	0.055
Proportions of elderly people	0.14	.016	
Proportion of one-person households	0.034	.554	
Proportion of people primary industry employment	0.035	.466	
Overall unemployment rate	0.001	.974	
Annual marriage rate	0.249	.000	
Annual temperature	−0.117	.003	
Annual total sunshine	0.15	.000	

Note: Multiple regression analyses predicting female suicide SMRs revealed that at the level of the crude model, there was no significant association between lithium levels and suicide SMRs. After adjustments (adjusted model 1), female suicide SMRs were still not significantly associated with lithium levels. The small value of adjusted R^2(0.055) indicates that the included factors such as lithium levels did not contribute to the variance in female suicide SMRs.

female populations, the adjusted model 1 showed significant inverse associations of lithium levels with total and male SMRs, but not with female SMRs. In the female adjusted model 1, the small value of adjusted R^2 (0.055) indicates that the included factors, such as lithium levels, did not contribute to the variance in female suicide SMRs. The non-significance of the association between lithium levels and suicide rates in the crude model may reflect the fact that suicide rates are affected by a variety of bio-psycho-social factors. The significant inverse associations observed in the adjusted model are consistent with our previous studies,[2-4] thus reconfirming that lithium levels in drinking water are inversely associated with suicide rates.

Regarding gender differences in the effect of trace lithium on suicide, findings have been conflicting, with several studies[2-4,12] reporting a significant inverse association with lithium levels in drinking water in males, whereas other studies[5,10] found an association in females. This so far the largest study in Japan that supports a male response to trace lithium. The reason for the male response is unknown, although, as suggested by Sher,[19] there are possibilities that higher levels of lithium in the drinking water decrease suicide rates among men by reducing impulsivity and aggression, and that suicidality is reduced by decreasing testosterone levels. In any case, lithium has superior anti-suicidal effects compared to other stabilizers,[20] and this effect may be effective at much lower levels than the so-called therapeutic lithium levels for mood-stabilizing effects (0.4-1.2 mEq/L).

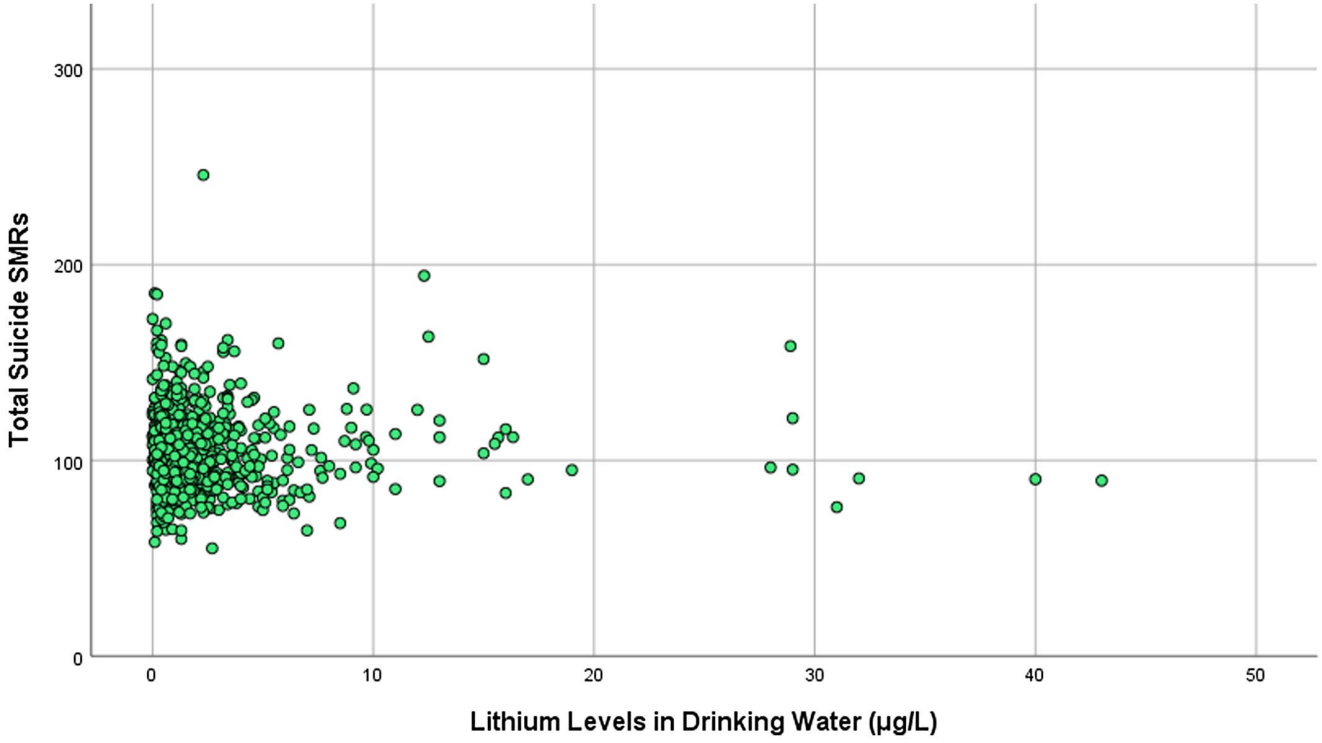

FIGURE 2 The association between lithium levels in drinking water and total suicide SMRs

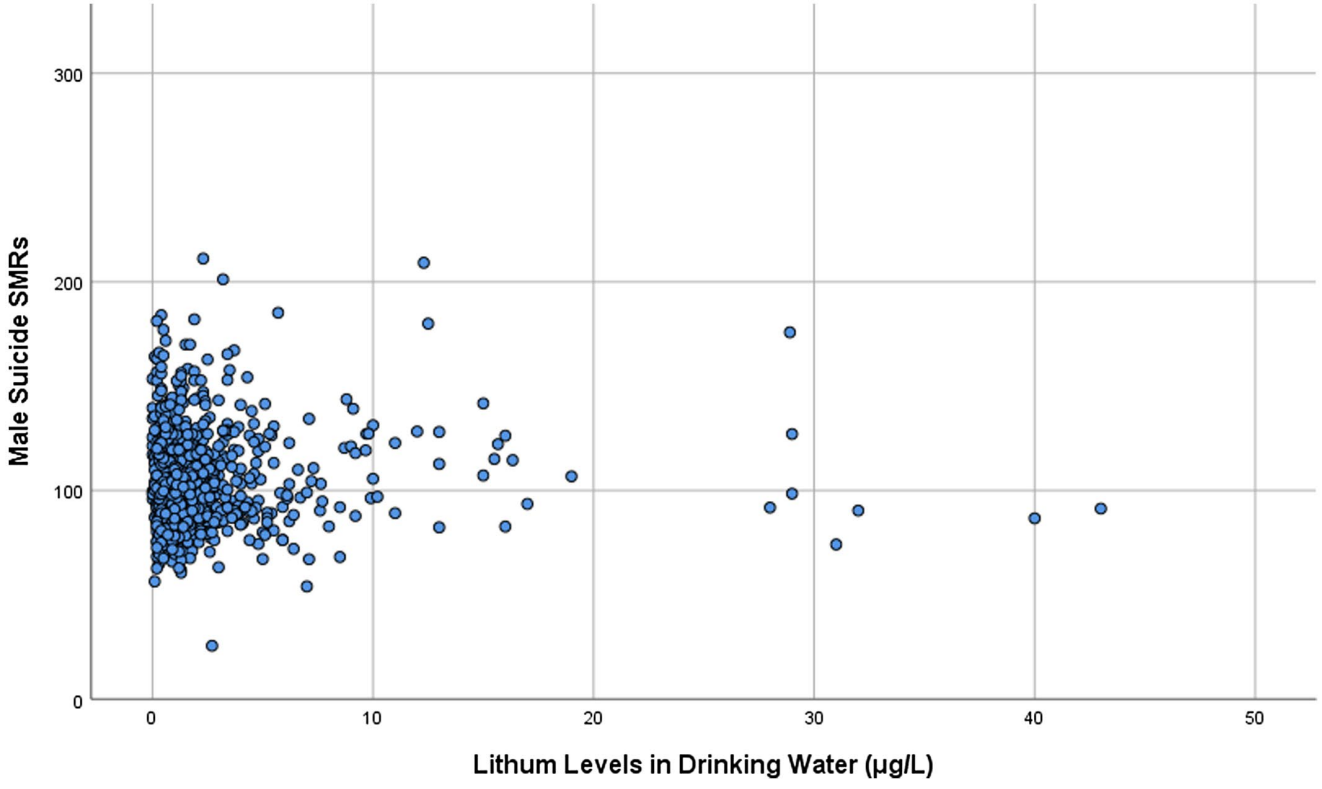

FIGURE 3 The association between lithium levels in drinking water and male suicide SMRs

Further adjustments using the mean proportions of residents who continued to live in each city (adjusted model 2) showed no change in the significant inverse association between lithium levels and total suicide SMRs. Probably due to the consistently high proportion of residents who continued to live in the 808 cities and wards (95.3%, range, 88.4-96.9), the effect of people moving out of the cities could not be

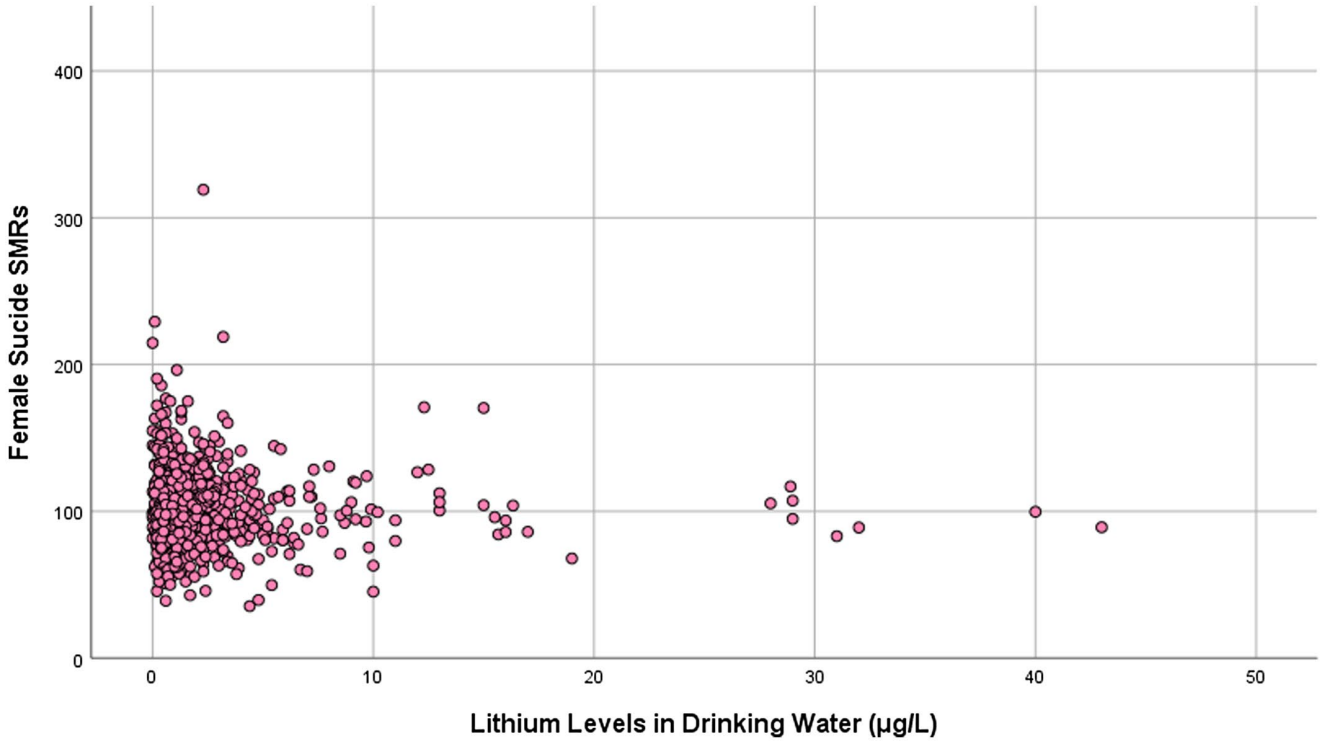

FIGURE 4 The association between lithium levels in drinking water and female suicide SMRs

appropriately measured. Conversely, our data showing a significant association between trace lithium and low suicide rates supports the effects of long-term exposure to trace lithium in the same place.

Limited to the 47 cities that had a prefectural office and provided data on the consumption of bottled water, the inverse association between lithium levels and total suicide SMRs was nearly significant in the adjusted tentative model. The lack of a clearly significant association may be due to the relatively small sample of cities. After adding the consumption of bottled water as a factor to the model, the value of β remained unchanged from that in the adjusted model 2, suggesting that the effect of the consumption of bottled water was very small. Japanese bottled water has in fact relatively low lithium levels (mean, 2.9 μg/L, range, 0-5.95) in comparison to imported bottled water (mean, 57.1 μg/L, range, 4.25-175.0),[21] almost identical to the mean lithium level in drinking water (2.39 μg/L). Moreover, even if residents drink bottled water, they use tap water for cooking. Therefore, at least in the present study, the effect of drinking bottled water may be negligible.

Finally, lithium levels of 30 μg/L or more may be associated with the lower suicide SMRs (less than 100) not only in total and male populations, but also in female populations, although this range has a very few number (only four) of cities. Clearly, further studies are required to reconfirm this exploratory speculation.

The limitations of the current study are due to methodological issues. In contrast with Knudsen et al,[13] who used individual-level register-based data on the entire Danish adult population (3.7 million individuals) and conducted spatial analyses using a Bayesian conditional autoregressive model to address spatial autocorrelation, we used multiple regression analyses following a previous method without spatial autocorrelation. Nonetheless, interestingly, our findings are partially in line with Knudsen et als' findings[13] reporting that suicide rate increased with lithium levels from 0.6 to 30.7 μg/L.

Apart from these epidemiological studies, Kanehisa et al[22] analyzed serum lithium levels of 199 patients including 31 patients with a history of suicide attempts, 21 patients engaging in self-harm, and 147 control patients. There was a significant difference between the three groups, with patients with a history of suicide attempts having significantly lower lithium levels than control patients; this was however only found in males, not in females. Moreover, multivariate logistic regression analyses with adjustments for age and gender showed the same pattern, suggesting that higher serum lithium levels may be protective against suicide attempts in lithium therapy-naive individuals.

In conclusion, the present findings reconfirm the inverse association between lithium levels in drinking water and suicide rates particularly in the male population who continue to live in the same city for a long time. Moreover, the effect of bottled water may be negligible and 30 μg/L or more of lithium levels in drinking water may be associated with lower suicide rates.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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