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Lithium in drinking water and Alzheimer's dementia: Epidemiological Findings from National Data Base of Japan

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Abstract

Objectives: The aim of this study was to investigate the association between lithium levels in drinking water and prevalence of Alzheimer's dementia (AD).

Methods: Lithium levels in the drinking water of 808 cities and wards (i.e., 785 Japanese cities of 46 prefectures and 23 wards of Tokyo) in Japan were examined in relation to the prevalence of AD during the 5 years from 2010 to 2014, which was calculated on the basis of the national data base of Ministry of Health, Labor, and Welfare of Japan. Multiple regression analyses were used to investigate the association of lithium levels with the prevalence of AD with adjustment for relevant factors (proportions of one-person households as a family factor and people in primary industry employment as a job factor, annual total sunshine hours as a meteorological factor, and total number of beds of psychiatric hospitals as a medical factor) in total, male, and female elderly populations.

Results: The adjusted model showed a significant inverse association of lithium levels with female, but not with male, or total prevalence of AD.

Conclusions: These findings suggest that higher lithium levels in drinking water may be associated with lower prevalence of AD in female, but not male, populations.

KEYWORDS
Alzheimer's disease, drinking water, epidemiological study, lithium, national data base

1 | INTRODUCTION

So far, data are accumulating that trace lithium may be effective for suicide prevention. Since an inverse association between lithium levels in drinking water and suicide rates had been reported in 27 Texas counties in the United States in 1990,[1] numerous studies investigated this association, including our own studies.[2–5] Recent meta-analyses[6–8] confirmed that higher lithium levels in drinking water may be associated with lower suicide rates.

Another intriguing theme is the possible association between lithium in drinking water and Alzheimer's dementia (AD). Although it is trace lithium in the form of gluconate or carbonate, rather than lithium found in drinking water, in 2013, Nunes et al.[9] randomized 113 patients with AD having Mini Mental State Evaluation (MMSE) scores of 9–21 to receive either lithium (300 μg/day; $n = 58$) or placebo ($n = 55$) treatments in a 15-month, randomized, placebo-controlled, double-blind trial in Brazil. The lithium group demonstrated no decline in their performance on the MMSE scores, compared to lower scores in the placebo group, suggesting the effects of trace lithium on AD.

In 2017, Kessing et al.[10] investigated whether the incidence of dementia in the general population covaried with long-term exposure to microlevels of lithium in drinking water in Denmark. A total of 73,731 patients with dementia and 733,653 controls (median age, 80.3 years) were included in the study. They showed that higher lithium levels in drinking water were nonlinearly associated with a lower incidence of dementia. In response to Kessing et al.,[10] in 2018, Parker et al.[11] used claim data for 4,227,556 adults living in 174 counties in the US. After adjustment for county-level demographics and health care resources, higher lithium levels were not significantly associated with lower prevalence of dementia. Thus, these reports provided conflicting findings.

In 2018, Fajardo et al.[12] conducted an epidemiological study to examine the relationship between lithium levels in drinking water and changes in AD mortality across several Texas counties. They showed a significantly inverse association between lithium levels in drinking water and changes in AD mortality, suggesting the effects of trace lithium on AD mortality.

Considering the abovementioned findings, the effects of lithium in drinking water on dementia are yet to be determined. Thus, the aim of this study was to investigate the association between lithium levels in drinking water and prevalence of AD.

2 | METHODS

2.1 | Study population

On March 31, 2010, Japan had 47 prefectures, consisting of 786 cities and the largest city—Tokyo—had 23 wards, each of which had a population as large as that of some other cities. Similar to our previous study about lithium levels in drinking water and suicide,[5] we decided to investigate these 808 regions, that is, all 785 cities and the 23 wards of Tokyo, for this study. It should be noted that all towns and villages were not included, but 91% of the Japanese population lived in cities and wards in 2015.

2.2 | Data of Alzheimer's dementia

We obtained anonymous claims about AD from a national data base via Nippon Telegraph and Telephone (NTT) data and the Ministry of Health, Labor, and Welfare of Japan. The data consisted of anonymous claims from two major medical insurances for elderly people: one for early elderly people (65 to 74 years old, approximately 16,800,000 people) and another for later elderly people (75 years old and older, approximately 18,200,000 people). Strictly speaking, there are other medical insurances for a small population of elderly people, but these data were unavailable. We collected the data of Alzheimer's disease as the G30 code of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) from the abovementioned two major medical insurances for elderly people during the five-year period from 2010 to 2014. Concurrently, to focus on the ≧65 population group, we requested the age-stratified number of the total insured persons of the two major insurances from 47 prefectures.

2.3 | Measurement of lithium levels in drinking water

From 2010 to 2015, 988 tap water samples (usually from the main rail station or municipal office) of each city and ward were collected mainly by us and analyzed by a third party using mass spectroscopy. The details were described in our previous paper.[5]

2.4 | Adjustment factors

We tried to adjust the crude association between lithium levels of drinking water and the prevalence of AD using four factors, which potentially affect the prevalence of AD: proportions of one-person households as a family factor, proportions of people in primary industry employment as a job factor, annual total sunshine hours as a meteorological factor, and total number of beds in psychiatric hospitals as a medical factor. The data on proportions of one-person households and people in primary industry employment were available for all 808 cities and wards, collected from the Statistics Bureau, Ministry of Internal Affairs and Communications—only for the years 2010 and 2015—as the Japanese national census is performed every 5 years. These data were not limited to elderly people but included elderly people. The mean of proportions of one-person households and proportions of people in primary industry employment in 2010 and 2015, corresponding with the census, was thus calculated for each individual city.

Data of annual total sunshine hours were partially available for 398 cities, from the Japan Meteorological Agency. The mean of the annual total sunshine hours in 2010 and 2015, corresponding with the census, was 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]

Finally, the total number of beds of psychiatric hospitals were available for the years 2010 and 2015 for all 808 cities and wards from the Statistics Bureau, Ministry of Internal Affairs and Communications. The mean of the total number of beds of psychiatric hospitals in 2010 and 2015, corresponding with the census, was calculated for each individual city.

2.5 | Statistical analysis

To calculate the prevalence of AD, we divided the number of AD patients estimated by the anonymous claims registered as G30 in the two major medical insurances for ≧65 year old from 2010 to 2014 by the number of population ≧65 years old in the individual

808 cities and wards from 2010 to 2014. We did not use the total number of insured persons ≧65 years old as a denominator because seven prefectures (Hokkaido, Yamagata, Mie, Osaka, Nara, Fukuoka, and Tochigi) did not provide the data of age-stratified insured persons and could not obtain the total insured persons ≧65 years old in these prefectures.

Similar to our previous studies,[2–5] 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 the association between the prevalence of AD (total, male, and female populations) and lithium levels in drinking water with the abovementioned adjustment factors.

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

3 | RESULTS

3.1 | Prevalence of Alzheimer's dementia

The mean total, male, and female prevalence of Alzheimer's dementia ≧65 years old for the 5 years (2010–2014) were 5.8% (SD 1.2), 4.4% (SD 0.9), and 6.8% (SD 1.4).

3.2 | Lithium levels in drinking water

The mean lithium level in drinking water was 2.39 μg/L (SD 4.0). The distribution of lithium levels was considerably skewed (skewness = 5.45; kurtosis = 38.89). We thus employed log-transformation to use parametric statistical procedures. The log-transformed lithium levels were not skewed (skewness = −0.059; kurtosis = 0.436), and the mean of log-transformed lithium levels was 0.95 (SD 0.49).

3.3 | Adjustment factors

The mean proportion of one-person households was 28.4% (SD 7.2), the mean proportion of people in primary industry employment was 5.9% (SD 5.8), the mean annual total sunshine was 1874.6 h (SD 192.4), and the mean of total number of beds of psychiatric hospitals was 389.9 (SD 653.0).

3.3.1 | Associations between the prevalence of AD and lithium levels

As shown in Table 1, at the level of the crude model, there was no significant association between the prevalence of AD and lithium levels in drinking water in the total populations (Figure 1). After adjustment for relevant factors (adjusted model), there was a significantly inverse association of the prevalence of AD with the mean annual total sunshine. Also, there were significantly direct associations of the prevalence of AD with the mean proportion of one-person households and the mean proportion of people in primary industry employment. There was no significant association of the prevalence of AD and lithium levels in drinking water or the mean of total number of beds of psychiatric hospitals in total populations.

As shown in Table 2, at the level of the crude model, there was no significant association between the prevalence of AD and lithium levels in drinking water in male populations (Figure 2). After adjustment for relevant factors (adjusted model), there was a significantly inverse association of the prevalence of AD with the mean annual total sunshine. Also, there were significantly direct associations of the prevalence of AD with the mean proportion of one-person households, the mean proportion of people in primary industry employment, and the mean of total number of beds of psychiatric hospitals. There was no significant association of the prevalence of AD and lithium levels in drinking water in male populations.

As shown in Table 3, at the level of the crude model, there was no significant association between the prevalence of AD and lithium levels in drinking water in female populations (Figure 3). After adjustment for relevant factors (adjusted model), however, there was a significantly inverse association of the prevalence of AD with lithium levels in drinking water and the mean annual total sunshine. Also, there were significantly direct associations of the prevalence of AD with the mean proportion of one-person households and the mean proportion of people in primary industry employment. There was no

TABLE 1 Association between lithium levels and prevalence of Alzheimer's dementia in total populations

Model	β	*p*	Adjusted R^2
Crude model			
Log-transformed lithium levels	−0.007	0.84	
Adjusted model			
Log-transformed lithium levels	−0.055	0.085	0.21
Annual total sunshine	−0.30	0.001	
Proportion of one-person households	0.25	0.001	
Proportion of people in primary industry employment	0.31	0.001	
Total number of beds of psychiatric hospitals	0.062	0.067	

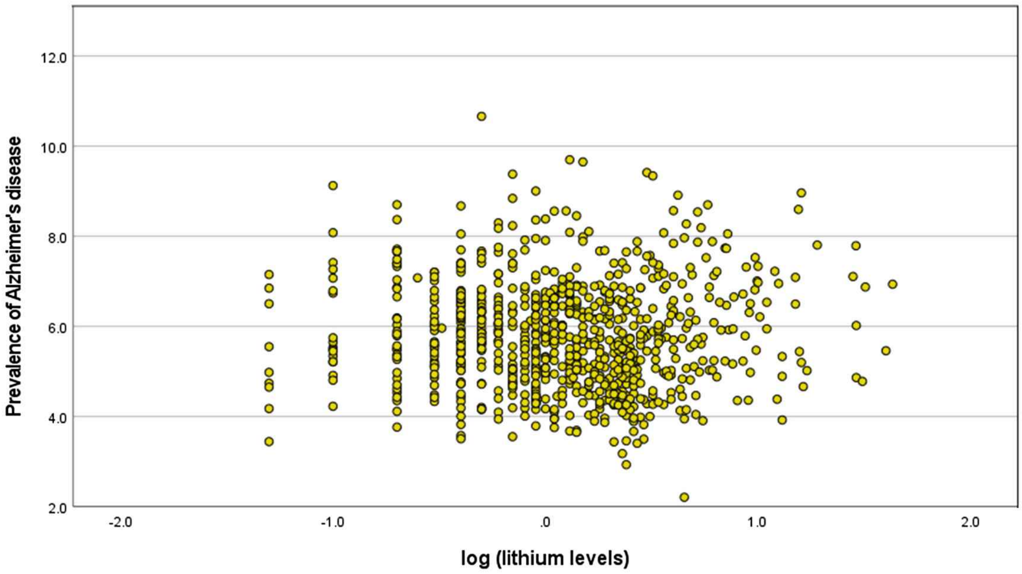

FIGURE 1 Association between lithium levels and prevalence of Alzheimer's dementia (%) in total populations.

TABLE 2 Association between lithium levels and prevalence of Alzheimer's dementia in male populations

Model	β	*p*	Adjusted R^2
Crude model			
Log-transformed lithium levels	0.009	0.79	
Adjusted model			
Log-transformed lithium levels	−0.036	0.26	0.21
Annual total sunshine	−0.30	0.001	
Proportion of one-person households	0.21	0.001	
Proportion of people in primary industry employment	0.31	0.001	
Total number of beds of psychiatric hospitals	0.074	0.031	

significant association of the prevalence of AD and the mean of total number of beds of psychiatric hospitals in female populations.

4 | DISCUSSION

Although our crude (unadjusted) model showed no significant association between the prevalence of AD and lithium levels in total, male, or female populations, the adjusted model showed a significant inverse association of lithium levels with the prevalence of AD in female, but not in male or total, populations. These findings suggest that higher lithium levels in drinking water may be associated with a lower prevalence of AD in female, but not in male or total, populations.

Regarding gender differences in the effect of trace lithium on dementia, we already reported significantly inverse associations of lithium levels in drinking water with suicide in male, but not in female, populations,[2–5] but this study showed a significantly inverse association of lithium levels in drinking water with the prevalence of AD in female, but not male, populations. The reason is unknown, but these are very interesting findings because lithium effects may be different due to disease and gender interaction.

As for adjustment factors, annual total sunshine was significantly and inversely associated with the prevalence of AD in total, male, and female populations. This is a robust association, and higher sunshine may be associated with lower prevalence of AD in both male and female populations. However, Ma et al. recently showed that there was a J-shaped correlation between outdoor sunlight exposure time and dementia risk.[13] Further studies are required to investigate the effects of sunlight on AD.

The proportion of one-person households was significantly and directly associated with the prevalence of AD in total, male, and female populations. Joyce et al.[14] showed that social isolation and a low social support are associated with worse cognitive function in women, but not men, which may be partially in agreement with the direct association between the proportion of one-person households and the prevalence of AD in our study, showing the association in both male and female populations.

Also, the proportion of people in primary industry employment was significantly and directly associated with the prevalence of AD in

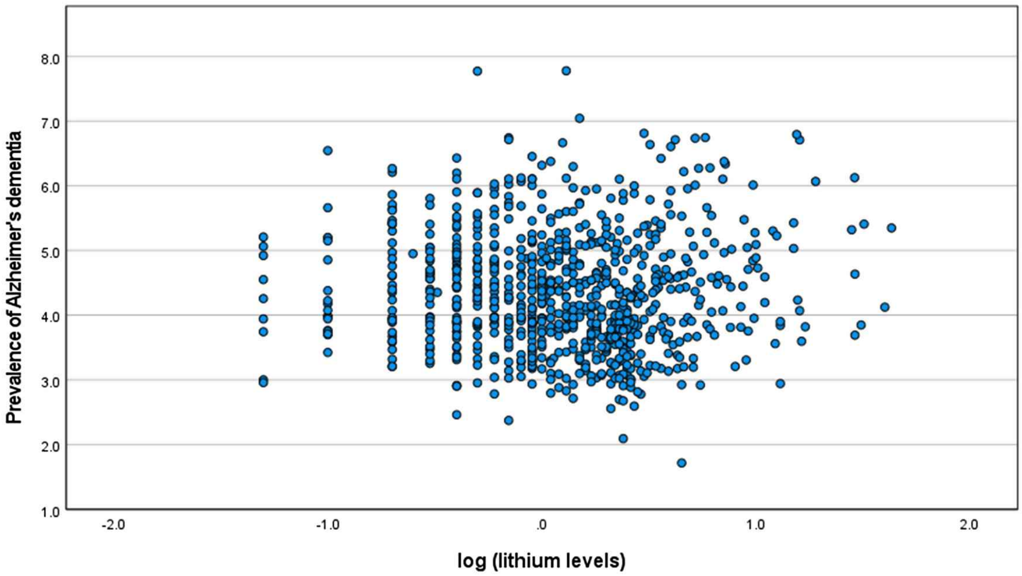

FIGURE 2 Association between lithium levels and prevalence of Alzheimer's dementia (%) in male populations.

TABLE 3 Association between lithium levels and prevalence of Alzheimer's dementia in female populations

Model	β	*p*	Adjusted R^2
Crude model			
Log-transformed lithium levels	−0.019	0.59	
Adjusted model			
Log-transformed lithium levels	−0.065	0.046	0.18
Annual total sunshine	−0.28	0.001	
Proportion of one-person households	0.25	0.001	
Proportion of people in primary industry employment	0.28	0.001	
Total number of beds of psychiatric hospitals	0.053	0.13	

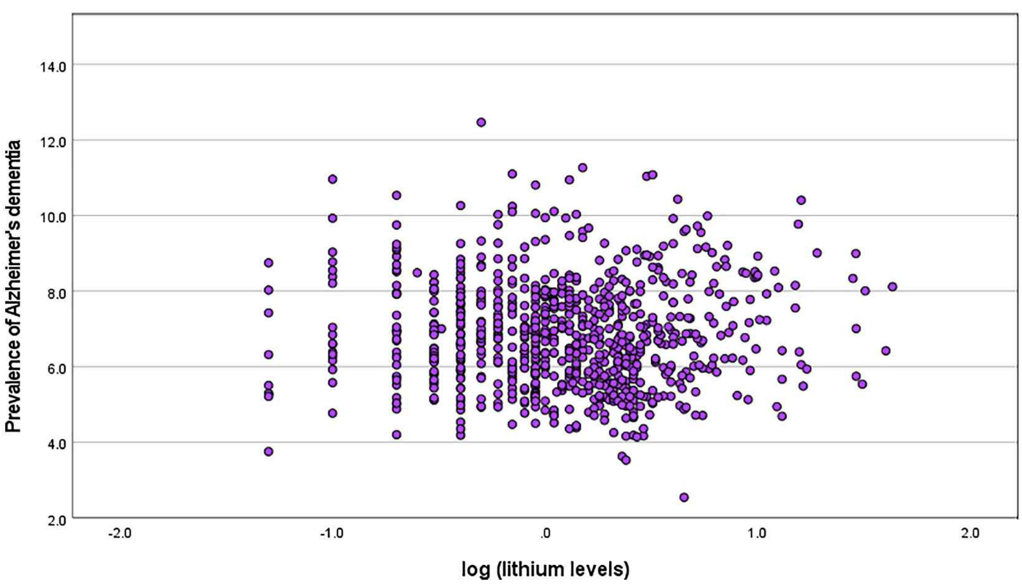

FIGURE 3 Association between lithium levels and prevalence of Alzheimer's dementia (%) in female populations.

total, male, and female populations. Nabe-Nielsen et al.[15] compared the effects of leisure-time physical activity and occupational physical activity. They revealed that participants with high occupational physical activity had a significantly higher incidence rate ratio of dementia than participants in sedentary jobs, whereas participants with high leisure-time physical activity had a non-significantly lower incidence rate ratio of dementia than participants in sedentary jobs, suggesting that leisure-time physical activity and occupational physical activity may be differentially associated with dementia. These findings are in concordance with our findings that a higher proportion of people in primary industry employment was significantly and directly associated with greater prevalence of AD because primary industry employment contains agriculture, forestry, fishery, and mining—which clearly require more occupational physical activity than other jobs.

Finally, the total number of beds of psychiatric hospitals was significantly and directly associated with the prevalence of AD in male, but not in female or total, populations, probably because more psychiatric beds may indicate more demand for psychiatric treatment, including dementia, resulting in the direct association between total number of beds of psychiatric hospitals and the prevalence of AD, although it is unknown why this is the case in male, but not female, populations.

There are several limitations. First, the data were somewhat old because we had collected tap water samples from 2010 to 2015 and tried to match the observational period of the prevalence of AD (2010–2014) and adjustment factors (2010 and 2015) to the tap water sampling period (2010 and 2015), although there was a small difference (1 year between 2014 and 2015) in the observational period of the prevalence of AD (2010–2014). Second, although we postulated a linear relationship between lithium levels and the prevalence of AD, Kessing et al.[10] showed a non-linear relationship. Further studies are required to determine the true nature of this relationship. Third, as previously mentioned, we could not obtain all anonymous claims due to the lack of data for other medical insurances covering a small population of patients with AD. Although this might have brought about underestimation of the prevalence of AD, the purpose of the present study was not to estimate the correct prevalence but rather investigate the association between lithium levels and prevalence. Fourth, there are possibilities that lithium concentrations in soil correlate with lithium concentrations in drinking water and that lithium concentrations in vegetables and grains grown on land correlate with high lithium concentrations in the soil. Of course, influence of the local diet is important. That is, lithium levels in drinking water is one of many resources building up serum lithium levels in a human body. Although we investigated the association between serum lithium levels and suicide,[16] at the moment, we do not have such data. Further studies are required to reconfirm the present findings in the association between serum lithium levels and dementia. Fifth, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are generally used more frequently by women, and it is possible that NSAIDs increased lithium blood concentrations and affected the results of this study. As for this study, we do not have the data regarding the intake of NSAIDs. Alternatively, using the data of our previous study,[16] we compared 68 female and 131 male serum lithium levels of 199 patients without a past or present history of lithium therapy. As a result, the mean female serum lithium level was 6.07 μg/L (SD = 3.6) and the mean male serum lithium level was 5.92 μg/L (SD = 4.2), which was not significantly different. Therefore, even if NSAIDs are generally used more frequently by women, at least in the sample, NSAIDs did not increase serum lithium levels in blood and probably did not affect the results of this study. Sixth, regarding drinking mineral water rather than drinking water, previously, we measured the lithium levels of mineral waters and compared those of Japanese mineral waters, those of foreign ones, and those of drinking water.[17] As a result, lithium levels of foreign mineral waters (57.1 μg/L, SD-69.0) were significantly higher than those of Japanese mineral waters (2.9 μg/L, SD = 2.3) (p = 0.011) and Japanese drinking waters at that time (2.5 μg/L, SD = 4.8) ($p < 0.001$), though there was no significant difference between Japanese mineral waters and drinking waters. Considering that a substantial part of Japanese probably drink mineral water, and if they drink, most of them drink Japanese mineral water, the influence of mineral water may be negligible, and actually many Japanese people may drink drinking water at least indirectly diet containing drinking water such as miso soup. Finally, the values of adjusted R^2 were small, suggesting that lithium levels in drinking water and the present adjustment factors could only account for a small part of the involvement in AD. Probably many factors, such as genetic factors, less education, hearing loss, hypertension, diabetes mellitus, obesity, smoking, depression, physical inactivity, and social isolation, may be associated with the onset of AD.[18] Further studies are necessary to comprehensively adjust for these relevant factors to investigate the association between trace lithium and AD prevalence.

In conclusion, these findings suggest that higher lithium levels in drinking water may be associated with lower prevalence of AD in female, but not male, populations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest regarding this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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