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Original Research

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Lithium Levels in Tap Water and the Mental Health Problems of Adolescents:
An Individual-Level Cross-Sectional Survey

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ABSTRACT

Objective: We investigated the association between lithium level in tap water and mental health problems, including depressive symptoms, anxiety, and aggressive and suicidal behaviors, in a general population of adolescents using a large individual-level dataset.

Methods: A school-based, cross-sectional survey was conducted in Kochi Prefecture in Japan between 2008 and 2009. Students in 24 public junior high schools were asked to anonymously complete a self-report questionnaire. The main outcome measures were mental health problems, including those on the 12-item General Health Questionnaire, interpersonal violence, bullying, destructive behavior, self-harm, and suicidal ideation. Samples were collected from sources that supplied drinking water to schools, and lithium levels were measured using atomic absorption spectrophotometry. The associations of lithium levels with mental health problems were examined using a generalized linear mixed model with schools as the fixed effect. Potential confounding factors were also added into the model.

Results: A total of 3,040 students among 3,311 students responded to the self-report questionnaire (response rate, 91.8%). The mean lithium concentration in tap water was 0.48 μg/L (SD = 0.52; range, 0.01 to 2.10; skewness = 2.01; kurtosis = 4.04), and it was relatively low compared with previous studies. In multivariable regression analysis, lithium level in tap water had an inverse association with depressive symptoms ($P = .02$) and interpersonal violence ($P = .02$) but not with suicidal behaviors (suicidal ideation, $P = .82$; self-harm, $P = .46$).

Conclusions: Lithium level in tap water was inversely associated with depressive symptoms and interpersonal violence among a general population of adolescents and may have antidepressive and antiaggressive effects.

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Many mental health problems that have their onset in adolescence[1] are the leading causes of disability-adjusted life-years in this age group.[2] Further, with the high potential of life-years lost by suicide,[3] suicide prevention in this group is a serious public health issue. In this context, a public health strategy is required to prevent mental health problems in adolescence.

Lithium could potentially be used to help minimize mental health problems in a large segment of the population. Lithium is a natural trace element that is dissolved in groundwater and drinking water[4] and has been widely used for the treatment of mood disorders because of its antisuicidal effects.[5,6] Previous ecological studies have reported an inverse association between lithium level in water and regional suicide and violent crime rates,[7–10] whereas other studies have reported no significant association between them.[11,12] Because these were ecological studies, the inconsistent results may be caused by an ecological fallacy (overestimation of the population association).[13] Only 1 individual-level study[14] on the association between lithium level in tap water and mental health has been reported, and no association between lithium levels in tap water and depressive symptoms was found. However, the study used a small sample of adults and classified lithium water levels into 3 categorical levels.[14]

To date, no individual-level study has been conducted on the relationship between lithium level in tap water and mental health problems in adolescents. Here we explored the association of lithium level in tap water with depressive symptoms, aggressive behaviors, and suicidal behaviors in a general population of adolescents in Japan using a large individual-level data set. We hypothesized that lithium level in tap water had an inverse association with mental health problems in adolescents.

METHODS

Study Design and Settings

The present study was a part of a school-based cross-sectional survey[15] that was conducted in Japan. The principal investigators approached all public junior high schools (students aged 12–15 years; seventh to

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Clinical Points

- No large-scale individual-level study has examined the association between lithium level in tap water and mental health problems in adolescents.
- This large individual-level study showed an inverse association between lithium level in tap water and depressive symptoms and interpersonal violence in a general adolescent population.
- The results support the potential of low-dose lithium therapy on depressive symptoms, anxiety, and aggression in adolescents.

ninth grade) in Kochi Prefecture, which had a population of approximately 790,000 between 2008 and 2009. The students were asked to answer the questionnaires and seal them in envelopes after completion. Before the survey, we informed parents of the survey via letter and asked them to notify the school if they did not want their child to respond. In addition, on the day of the survey, students could opt out of the survey. The students were told that their participation was anonymous and voluntary and no disadvantage would occur due to nonparticipation. We included all data from the students who answered the survey except from those who were from schools with less than 5 students. We excluded those schools from the analysis because the opportunities for bullying and interpersonal violence were much fewer than those in other schools. This study was approved by the ethics committee of Kochi Medical School and the Tokyo Metropolitan Institute of Medical Science.

Measures

The self-report questionnaires included items concerning the following: (1) depressive symptoms (the Japanese version of the 12-item General Health Questionnaire [GHQ-12][16]); (2) aggressive behaviors, such as interpersonal violence, bullying, and destructive behavior; (3) suicidal behaviors, including suicidal ideation and self-harming behavior; and (4) other variables, including demographic characteristics.

Depressive symptoms. The GHQ-12,[16] which is one of the most widely used self-report screening tools for anxiety and depressive symptoms occurring in the previous month, was originally applied to adult populations and later used and validated for younger groups.[15] The response options are "less than usual," "no more than usual," "rather more than usual," or "much more than usual." As in previous studies,[15] we assigned 1 point for "rather more than usual" or "much more than usual" and 0 points for other responses. The sums of each of the questions ranged from 0 (good mental health) to 12 (poor mental health).

Aggressive behaviors. Interpersonal violence, bullying, and destructive behavior in the previous year were determined from the questions, "Have you physically abused someone in your family or your friends during the previous year?" "Have you bullied someone during the previous year?" and "Have you been extremely frustrated and damaged something during the previous year?" The response options were "no" or "yes," and the latter response indicated aggressive behaviors. We referred to the items in the Rutter Behavior Scales[17] and applied similarly simple wordings to avoid misunderstanding of questions.

Suicidal behaviors. Current suicidal ideation was determined by the question, "Have you thought that your life was no longer worth living during the previous month?" The response options were "no," "probably no," "possibly yes," or "yes." We defined the individuals who answered yes as those who had suicidal ideation. Self-harming behavior was determined by the question, "Have you intentionally hurt yourself within the past year?" The response options were "no" or "yes." Respondents who answered yes were asked to provide a description of the actual method of self-harm. On the basis of a previous study,[18] self-harm was defined as a nonfatal act in which an individual deliberately did 1 or more of the following: (1) initiated behavior (eg, self-cutting, jumping from a height) intending to cause self-harm, (2) ingested a substance in excess of the prescribed or generally recognized therapeutic dose, or (3) ingested a noningestible substance or object. Identification of deliberate self-harm episodes was based on independent ratings by 2 raters. The κ value for interrater agreement was 0.83 (95% confidence interval [CI] = 0.79–0.86).

Other variables. The potential confounders included age, sex, number of students in school, and living with parents. Because lithium levels in tap water can differ between regions, factors that could be associated with both region and mental health problems were considered as potential confounders.

Tap-water sampling and measurement of lithium concentrations. Water samples were collected from the water sources that supplied tap water to each student's residential area in Kochi Prefecture. If there was more than 1 water source for a school, the average concentration of the water sources was determined. Lithium levels in tap water were measured using atomic absorption spectrophotometry (Hitachi z-9000) at Kochi University. The detection limit for lithium was 0.01 μg/L.

Statistical Analysis

Similar to previous studies,[11,12] because the distribution of lithium levels was skewed (skewness = 2.01; kurtosis = 4.04), the relationship between lithium concentrations in tap water and mental health–related variables was analyzed by logarithmic transformation (LogLithium). We analyzed the associations of lithium concentrations with depressive symptoms, interpersonal violence, bullying, destructive behavior, and suicidal behaviors independently by using a generalized linear mixed model (GLMM) with schools as the fixed effect. In the adjusted model, potential confounders were also added to the GLMM. P values $< .05$ were taken as indicating statistical significance. Descriptive and regression analyses were performed by using SPSS, version 20.0 (IBM, Armonk, New York).

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Table 1. Demographic Characteristics and the Prevalence of Mental Health Problems of the Participants in This Study[a]

Variable	Total (n = 3,040)	Male Participants (n = 1,551)	Female Participants (n = 1,489)	*P* Value[b]
Age, mean (SD), y	13.7 (0.9)	13.6 (0.9)	13.7 (0.9)	.06
Living with parents, n (%)	2,377 (78.2)	1,208 (77.9)	1,169 (78.5)	.68
Depressive symptoms,[c] mean (SD)	2.98 (3.04)	**2.35 (2.78)**	**3.62 (3.17)**	<.01**
Interpersonal violence, n (%)	839 (27.6)	**493 (31.8)**	**346 (23.2)**	<.01**
Bullying, n (%)	428 (14.1)	**255 (16.4)**	**173 (11.6)**	<.01**
Destructive behavior, n (%)	1,077 (35.4)	532 (34.2)	545 (36.6)	.16
Suicidal ideation, n (%)	115 (3.8)	**45 (2.9)**	**70 (4.7)**	<.01**
Self-harming behavior, n (%)	111 (3.7)	**14 (0.9)**	**97 (6.5)**	<.01**

[a]Boldface is used for variables that showed *P* values < .05.
[b]Two-tailed *t* tests.
[c]Total score of the 12-item General Health Questionnaire.
**$P < .01$.

Table 2. Associations Between Lithium Levels in Tap Water and Depressive Symptoms, Aggressive Behaviors, and Suicidal Behaviors[a]

Variable	Unadjusted β	Unadjusted SE	Unadjusted *P* Value	Adjusted[b] β	Adjusted[b] SE	Adjusted[b] *P* Value
Depressive symptoms[c]	**−0.22**	**0.10**	**.02***	**−0.23**	**0.09**	**.02***
Interpersonal violence	**−0.36**	**0.15**	**.01***	**−0.34**	**0.15**	**.02***
Bullying	0.11	0.22	.62	0.15	0.23	.51
Destructive behavior	−0.15	0.14	.28	−0.14	0.14	.32
Suicidal ideation	−0.06	0.30	.85	−0.06	0.28	.82
Self-harming behavior	−0.17	0.28	.54	−0.20	0.27	.46

[a]Boldface is used for variables that showed *P* values < .05. Missing data were excluded in each statistical analysis. Statistical significance was set at .05. Lithium concentration was transformed to its logarithm in the statistical analysis.
[b]Adjusted for age, sex, number of students in school, and living with parents.
[c]Total score of the 12-item General Health Questionnaire.
*$P < .05$.

RESULTS

Descriptive Statistics

All cities except Kochi City in Kochi Prefecture allowed water sample collection, and all 25 public junior high schools in those cities agreed to participate in the survey. Because 1 school had only 1 student, we excluded this school from further analysis and finally used the data from 3,311 students in 24 schools (mean [SD] n = 127 [116]). Of the 3,311 students, 3,040 students (91.8%) gave analyzable responses (absent, n = 200; response refusal, n = 71; males, n = 1,551 [51.0%]). Their mean (SD) age was 13.7 (0.9) years (range, 12–15).

The demographic characteristics, mean GHQ-12 score, and presence of interpersonal violence, bullying, destructive behavior, self-harming behavior, and suicidal ideation are summarized in Table 1. Because 2 water samples had lithium concentrations below the detection limit of 0.01 μg/L, this value was assigned as the lithium concentration for further analysis. The mean (SD) lithium concentration in tap water was 0.48 (0.52) μg/L (range, 0.01 to 2.10; skewness = 2.01; kurtosis = 4.04) and LogLithium was −0.57 (0.57) (range, −2.00 to 0.32; skewness = −1.11; kurtosis = 1.86).

Association Between Lithium Concentration and Mental Health

A higher LogLithium was associated with lower depressive symptoms (unadjusted: β = −0.22, 95% CI = −0.42 to −0.02, $P = .02$; adjusted: β = −0.23, 95% CI = −0.41 to −0.05, $P = .02$; Table 2). Similarly, a higher LogLithium was significantly associated with reduced prevalence of interpersonal violence (unadjusted: β = −0.36, 95% CI = −0.65 to −0.07, $P = .01$; adjusted: β = −0.34, 95% CI = −0.63 to −0.05, $P = .02$). On the other hand, bullying, destructive behavior, suicidal ideation, and self-harming behaviors were not associated with lithium concentration or LogLithium in both unadjusted and adjusted models.

DISCUSSION

Principal Findings

To the best of our knowledge, this study is the first to show that lithium levels in tap water had small but significant inverse associations with depressive symptoms and interpersonal violence in a general population of adolescents by using a large individual-level data set.

Possible Explanations

The present study showed an inverse association between lithium water levels and self-reported depressive symptoms in adolescents. A previous study[14] suggested that there was no association between lithium level in tap water and depressive symptoms; however, that study compared the mean depression levels in 3 groups of adults defined by lithium levels and did not conduct individual-level analysis of the association between depression and lithium levels. The results of the present study are consistent with those of previous clinical studies that supported the effectiveness of lithium augmentation therapy for mood disorders.[6] Although there has been little evidence for the effectiveness of lithium monotherapy on depressive episodes,[19] the results of this study suggest that lithium in tap water has antidepressive effects.

An inverse association between lithium water levels and interpersonal violence in adolescents was observed in this study. This observation was consistent with those in previous ecological studies that showed an inverse association between lithium water levels and regional homicide[20] or crime rates.[12] Our study, which used a large individual-level data set, adds further evidence for an inverse association between lithium water levels and violent behaviors in adolescents. The inverse association between lithium level in tap water and interpersonal violence shown in this study also accords with a previous review that suggested lithium's effects on decreasing aggression and impulsivity.[21]

Although no association between lithium water levels and suicidal ideation or self-harming behavior was observed, there are 2 possible explanations for this observation. First, the lithium water levels in this study were relatively

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low. Similar nonassociations between water levels and the regional suicide rate have been reported in a previous study,[11] whereas several studies have suggested a significant inverse association between lithium water levels and suicide rate.[7–10] Because the lithium water levels in the present study were similar to those in the study[11] that found no association and relatively lower than those in the 4 studies[7–10] that did find associations, the preventive effects on suicide may be caused by specific lithium levels. Although several clinical studies[5,22] have shown the effectiveness of lithium on suicide prevention in patients with mood disorders, a previous study[23] suggested that the lithium effectiveness on suicide prevention depended on the dose. Second, the definition of suicidality used in this study possibly attenuated the association with lithium exposure. The suicidal ideation question asked about ideation in the past month, whereas the 4 aggressive-behaviors questions asked about behaviors in the past year. This difference could have underestimated suicidal ideation and reduced the power for detecting an association between suicidal ideation and lithium levels. In addition, because we used a conservative definition of suicidal ideation by considering "possibly yes" to be the same as "no," this interpretation might have attenuated the association.

The biological mechanisms underlying the effect of lithium on aggression and depression are unclear, but a neuroprotective property of lithium has been proposed. Antiapoptotic genes have been shown to be up-regulated and proapoptotic genes to be down-regulated in lithium responders relative to the expressions in nonresponders.[24] Further, a study[25] involving inpatients with bipolar disorder showed that long-term lithium treatment was associated with increased gray matter volumes in the same areas, whereas suicide attempts were associated with decreased gray matter volumes.

Implications

There are 2 implications of the results obtained in this study. First, promoting intake of lithium-rich foods and water could be a potential public health strategy to minimize mental health problems in adolescents if no adverse effects are observed in further studies. Second, although the study results were obtained from a nonclinical survey using self-reported measurement of mental health problems, the results suggest the potential of low-dose lithium therapy for treatment of depressive symptoms and aggression in adolescents.

Strengths and Weaknesses

This study was the first to examine the association between lithium levels in tap water and mental health problems in adolescents by using a large individual-level data set. In addition, because the response rate was very high in this study, generalizability of the results should be high. Nonetheless, this study had several limitations. First, data were not obtained on lithium intake from food, which generally exceeds that from drinking water.[4] Second, we did not collect data on the use of bottled water, which possibly contains more lithium than tap water. However, Japanese people drink tap water more than bottled water[26]; thus, use of bottled water may not be a significant factor. Third, we could not obtain the economic status of each student. However, because the land price and socioeconomic status of families were similar within regions and students were assigned to the nearest public junior high schools in Japan, the use of schools as the fixed effect might compensate for this limitation to some extent. Fourth, we did not collect information on the use of psychotropic medications that could have affected mental health problems. Fifth, the reliability and validity of the measurements of aggressive behaviors have not been established. The query about "physical abuse against family or friends" may have underestimated interpersonal violence because the participants may not have reported violence against peers who were not their friends. However, we applied simple wordings, such as those used in the Rutter Behavior Scales, to avoid misunderstandings of the questions,[17] and the prevalence of bullying in this study was within the range reported in a large international survey.[27] Sixth, the large size of the sample may have led to finding associations between lithium and the outcome variables that were statistically significant but not clinically significant. Future studies should examine lithium intake both from food and water. In addition, an individual-level study should be considered in an area where the lithium concentration in tap water is higher than the concentrations in the water of the sites in this study.

CONCLUSION

Lithium levels in tap water were inversely associated with depressive symptoms and interpersonal violence in a general adolescent population. Thus, lithium in tap water may have antidepressive and antiaggressive effects. A future individual-level study is warranted to examine the association between mental health problems and lithium intake from both food and water in regions where the lithium concentration of tap water is higher than those of the sites in this study.

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Author contributions: Dr Nishida had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

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