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Lithium levels in tap water and psychotic experiences in a general population of adolescents

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ABSTRACT

Recently, several epidemiologic studies have reported that lithium in drinking water may be associated with lower rates of suicide mortality, lower incidence of dementia, and lower levels of adolescents' depression and aggression at the population level. However, to our knowledge, no study has investigated lithium level in tap water in relation to psychotic experiences in a general population of adolescents. This is the first study to investigate this using a large dataset. Information on psychotic experiences, distress associated with these experiences, and depressive symptoms were collected in 24 public junior high schools in Kochi Prefecture in Japan. Samples were collected from sources that supplied drinking water to schools, and lithium levels were measured using atomic absorption spectrophotometry. The association of lithium levels with psychotic experiences, considering distress as a degree of severity, was examined using an ordinal logistic regression model with schools and depressive symptoms as random effects. In total, 3040 students responded to the self-reporting questionnaire (response rate: 91.8%). Lithium levels in tap water were inversely associated with psychotic experiences ($p = 0.021$). We concluded that lithium level in tap water was inversely associated with psychotic experiences among a general population of adolescents and may have a preventive effect for such experiences and distress.

1. Introduction

Lithium is widely used for treating bipolar disorder and other mental disorders because of its mood-stabilizing and anti-suicidal effects and the improvements in impulse control associated with its use (Cipriani et al., 2013; Crossley and Bauer, 2007). It is a natural trace element found in ground and drinking water, and its concentrations can vary widely depending on the geographic region (Concha et al., 2010; Schrauzer, 2002). Evidence from ecological studies indicate that the lithium concentration in drinking water may be inversely associated with the regional rates of suicide (Helbich et al., 2012; Kapusta et al., 2011; Ohgami et al., 2009), crime rates (Dawson et al., 1972; Schrauzer and Shrestha, 1990), and mental health service use (Dawson et al., 1972). In addition to evidence from these ecological studies, recent studies using individual-level datasets have also revealed a significant inverse association between lithium levels in tap water and incidence of dementia among a nationwide elderly population, as well as between these levels and depressive symptoms and interpersonal violence among a general adolescent population (Ando et al., 2017; Kessing et al., 2017). These results imply that promoting the intake of lithium-rich water could be a potential public health strategy to minimize mental health problems in the community.

Psychotic experiences, associated with attenuated hallucinatory and delusional symptoms, are far more common in the population than are frank psychosis (van Os et al., 2009). They are usually transient and only a small percentage (8–10%) of such episodes evolves into psychotic and nonpsychotic disorders each year (Kaymaz et al., 2012). However, psychotic experiences are associated with a wide variety of clinical symptoms, including depression, anxiety, and suicidal problems, especially in the younger population (DeVylder et al., 2015; Kelleher et al., 2017; Nishida et al., 2010). A recent longitudinal cohort study demonstrated that psychotic experiences signify an elevated risk for persistence of suicidal ideation from mid-adolescence into late adolescence and early

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adulthood (Kelleher et al., 2014). These results imply that psychotic experiences in adolescents could be an interventional target to reduce the risk of subsequent mental health problems and suicide.

To the best of our knowledge, only one study investigated lithium levels in tap water in relation to psychotic outcomes among the general population. This epidemiological study conducted in the late 1960s in Texas, USA, demonstrated that counties with higher water lithium levels had a lower rate of state mental hospital admissions of people diagnosed with schizophrenia and other psychotic disorders (Dawson et al., 1972). However, the regional rate of hospital admission was dependent on help-seeking; therefore, it did not allow for true population-based epidemiological enquiry of psychotic phenomena.

This is the first study to investigate lithium levels in tap water in relation to psychotic experiences in the general adolescent population using a large dataset. The study design also aimed to investigate the relationship between lithium level in tap water and "distressing" psychotic experiences, while controlling for the effect of confounders. A recent longitudinal study of healthy individuals with psychotic experiences revealed that those with psychotic experiences with statistically significantly distress at baseline were more likely to require mental health care in later life, compared to those with "non-distressing" psychotic experiences (Daalman et al., 2016). If lithium-rich water could mitigate the severity of such experiences, as assessed by distress, it might be able to reduce the need for mental health care and save the related cost in the community. Our hypotheses were: in the general population of adolescents, (1) lithium-rich tap water would reduce the risk of psychotic experiences and (2) it would also mitigate the distress by the experiences.

2. Methods

2.1. Study design and settings

The present study was part of a school-based cross-sectional survey that was conducted in Japan. Between 2008 and 2009, the principal investigators approached all public junior high schools (participants' ages: 12–15 years; seventh to ninth grade) in the Kochi Prefecture (108 public junior high schools), with a population of approximately 790,000. Of these, 25 public junior high schools agreed to participate in the survey. Because one of the schools had only one student, we excluded it from our study due to the difficulty to protect his/her anonymity; therefore, we used data from 3311 students in 24 schools (average number of students = 127, SD = 116, range: 19–439).

Students were asked to answer questionnaires and seal them in envelopes after completion. Prior to the survey, parents were informed of the survey via letter and asked to notify the school if they did not want their child to participate. This study received ethical approval for the use of an opt-out methodology based on the study characteristics of anonymous and voluntary. In addition, on the day of the survey, students were given the opportunity to opt out of the survey. Students were informed that their participation was anonymous and voluntary, and no disadvantage would be incurred due to non-participation. Of the 3311 students, 3040 students provided analyzable responses (valid response rate: 91.8%, absent = 200, incomplete responses = 71; boys = 1551 (51.0%); mean age = 13.7 years, SD = 0.9). There were no inclusion or exclusion criteria for the data other than incomplete responses. This study was approved by the ethics committee of the Kochi Medical School and the Tokyo Metropolitan Institute of Medical Science.

2.2. Tap water sampling and measurement of lithium concentrations

Water samples were collected from 109 water sources that supplied tap water to each student's residential area in the Kochi Prefecture. If there was more than one water source for a school, the average concentration of lithium of all the relevant water sources was determined. Lithium levels in the tap water were measured using atomic absorption spectrophotometry (z-9000, Hitachi High-Technologies Co. Ltd., Tokyo, Japan). The detection limit for lithium was 0.01 μg/L. Because two water samples were below the detection limit, 0.01 μg/L was assigned as the lithium concentration for those samples. Similar to previous studies (Gonzalez et al., 2008; Kabacs et al., 2011), because the distribution of lithium levels was skewed, lithium concentrations were analyzed using a logarithmic transformation. The average raw and logarithmic lithium concentrations in tap water were 0.48 μg/L (SD, 0.52; range, 0.01 to 2.10; skewness, 2.01; kurtosis, 4.04) and − 0.57 (SD, 0.57; range, −2.00 to 0.32; skewness, −1.11; kurtosis, 1.86), respectively.

2.3. Measures

The self-reporting questionnaires included items concerning psychotic experiences and potential confounding variables, including age, sex, school, living with parents, and depressive symptoms.

2.3.1. Psychotic experiences

Past psychotic experiences were assessed using four items adopted from the schizophrenia section of the Diagnostic Interview Schedule for Children (Costello et al., 1985; Costello et al., 1982). These items were previously used in a birth cohort study and found to be good predictors of schizophrenia spectrum disorder in adulthood (Poulton et al., 2000). The items were: (1) "Some people believe that their thoughts can be read. Have other people ever read your thoughts?" (2) "Have you ever had messages sent especially to you through the television or radio?" (3) "Have you ever thought that people are following you or spying on you?" (4) "Have you ever heard voices that other people cannot hear?" Possible responses were: "no" and "yes, probably," which were both taken to signify non-occurrence of the particular experience, and "yes, definitely (only once or more than once)," signifying a definite occurrence of the experience. We defined "adolescents with psychotic experiences" as adolescents who reported at least one type of psychotic experience (Nishida et al., 2010; Nishida et al., 2014). For adolescents with psychotic experiences, we also asked the following question: "When you experienced (reported experience), did you find it distressing or did it not bother you?" Possible responses were: "it did not bother me," "it bothered me a little," or "it bothered me a lot." The responses "it bothered me a little" or "it bothered me a lot" were defined as having "distressing" psychotic experiences (Kelleher et al., 2015).

2.3.2. Covariates

We considered age (Protano et al., 2018; Kelleher et al., 2012a, 2012b), sex (Shiotsuki et al., 2016), and socioeconomic status (Loch et al., 2017) as potential confounding factors when investigating the association between lithium levels in tap water sources and psychotic experiences among school students. Because students in Japan are assigned to the nearest public junior high school, the price of the land on which the student's house was built was assumed to be similar to that of his/her school. Therefore, the socioeconomic status of each student was determined by the appraised value of the land nearest to each school, which was determined by the land values in the Land Price Publication Act in 2011 in Japan (http://www.pref.kochi.lg.jp/soshiki/170301/). We included depression as a mediating factor in our analysis. Our previous study revealed that lithium levels in tap water sources were associated with depression among adolescents (Ando et al., 2017), and another study indicated that depression increases the risk of later psychotic experiences (Jaya et al., 2017). Depressive symptoms were assessed using the Japanese version of the 12-item General Health Questionnaire (GHQ), one of the most widely used self-reporting screening tools for anxiety and depressive symptoms occurring in the previous month (Ando et al., 2013; Goldberg et al., 1976). The response options were: "less than usual," "no more than usual," "rather more than usual," or "much more than usual." Any other

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responses were awarded 0 points. The sum of scores for each of the questions ranged from 0 (good mental health) to 12 (poor mental health).

2.4. Statistical analyses

To explore the effect of lithium concentration on the incidence of psychotic experiences, we employed a generalized linear mixed model (GLMM) for lithium concentration as an independent variable. The first model (Model 1) directly tested associations between lithium levels in tap water sources and psychotic experiences among adolescents. The second model (Model 2) adjusted for potential confounding factors, including age, sex, and socioeconomic status. In the third model (Model 3), we additionally adjusted for depression (GHQ-12 score) as a mediating variable. To consider the potential differences in the association between dependent and independent variables among schools, we set a random effect of school for the intercept of all models. For Model 3, we also added another random effect of school for the slope of the GHQ-12 score. To further explore the effect of lithium concentration on distressing psychotic experiences, an ordinal logistic regression model with random effects was employed, using psychotic experiences as a dependent ordinal variable (0 = no psychotic experiences, 1 = psychotic experiences without distress, and 2 = psychotic experiences with distress). We further tested whether lithium concentration was associated with the occurrence of psychotic experiences or associated distress. The GLMMs were estimated using the "glmer" function in the "lme4" package, and the ordinal logistic regression models using "clmm" function in "ordinal" package for R, version 3.4.1. The logit model in binomial distribution was applied for the estimation. A p value <0.05 was considered significant.

3. Results

Demographic characteristics are shown in Table 1.

A GLMM showed that lower lithium concentration was associated with the occurrence of psychotic experiences when adjusting for confounding and mediating variables ($p = 0.021$), although the association was in a trend level in a non-adjusted model ($p = 0.061$) (Table 2). In Model 3, the odds ratio and 95% confidential interval was 0.69 (0.51–0.95). This means that if lithium concentration in tap water would increase 10 times higher, the risk of psychotic experiences would decrease by 31%.

Table 1
Demographic characteristics and the prevalence of psychotic experiences among the participants in the study.

Variables	Total $n = 3040$	
Male (%)	1551	(51.0%)
Age (SD), years	13.7	(0.9)
Socioeconomic status[a] (SD), 1000 JPY/m^2	40.5	(22.7)
Affective symptoms[b] (SD)	2.98	(3.04)
Psychotic experiences		
Any psychotic experiences (%)	492	(16.4)
With distress (%)	272	(9.1)
Mind reading (%)	43	(1.4)
With distress (%)	13	(0.4)
Special message (%)	16	(0.5)
With distress (%)	2	(0.1)
Persecution (%)	205	(6.9)
With distress (%)	162	(5.4)
Verbal hallucination (%)	358	(12.0)
With distress (%)	134	(4.5)

Abbreviations: SD, standard deviation; JPY, Japanese Yen.
[a] Socioeconomic status of each student was determined by the appraised value of the land nearest to each school, determined by the land values included in the Land Price Publication Act in 2011 in Japan.
[b] Affective symptoms were measured by the total score of the 12-item General Health Questionnaire.

Table 2
Associations between lithium levels in tap water and psychotic experiences.
Dependent variable: Psychotic experiences with or without distress vs. No psychotic experiences (reference).

	Model 1		Model 2		Model 3	
Independent variables:	*B*	*p*-Value	*B*	*p*-Value	*B*	*p*-Value
Lithium levels in tap water	**−0.36**	**0.061**	**−0.36**	**0.048**	**−0.37**	**0.021**
Age			−0.23	<0.001	−0.30	<0.001
Sex			0.50	<0.001	0.21	0.051
Socioeconomic status			−0.0009	0.85	−0.002	0.61
Affective symptoms (GHQ-12)					0.26	<0.001

Model 1: Unadjusted model.
Model 2: Model adjusted for age, sex, and socioeconomic status.
Model 3: Model adjusted for age, sex, socioeconomic status, and affective symptoms measured by the total score of the 12-item General Health Questionnaire (GHQ-12).
We set a random effect of school for the intercept of all models. For Model 3, we added another random effect of school for calculating the slope of the GHQ-12 score.
Missing data (absent = 200, incomplete answers = 71) were excluded from statistical analysis. Analyzable responses were provided by 3040 students (valid response rate: 91.8%).
Bolded values showed 5% significance.
B, beta coefficients.

An ordinal logistic regression model also showed an inverse association between lithium concentration and having any psychotic experiences and those with distress, after controlling for confounding and mediating variables ($p = 0.043$) (Table 3). A GLMM showed that lower lithium concentration was associated with psychotic experiences with distress compared to those without any psychotic experiences or psychotic experiences without distress as reference (Table 3).

4. Discussion

To the best of our knowledge, this study is the first to show that lithium levels in tap water have a significant inverse association with psychotic experiences in a general adolescent population, using a large dataset. Only a previous study that was conducted in the late of 1960s in Texas investigated the association between the lithium levels in tap water and psychosis. A significant correlation was found between municipal drinking water lithium levels and rates of admission of people diagnosed with schizophrenia and other psychosis to state mental hospitals (Dawson et al., 1972). However, because it was an ecological study, there was a possibility of overestimation of the population association ("ecological fallacy") (Robinson, 2009). Our study overcomes

Table 3
Associations between lithium levels in tap water and psychotic experiences.
Dependent variable: Psychotic experiences with distress vs. No psychotic experiences or psychotic experiences without distress (reference).

	Model 1		Model 2		Model 3	
Independent variables:	*B*	*p*-Value	*B*	*p*-Value	*B*	*p*-Value
Lithium levels in tap water	**−0.50**	**0.009**	**−0.49**	**0.010**	**−0.38**	**0.043**
Age			−0.17	0.027	−0.27	0.001
Sex			0.89	<0.001	0.62	<0.001
Socioeconomic status			0.0008	0.88	0.002	0.63
Affective symptoms (GHQ-12)					0.28	<0.001

Model 1: Unadjusted model.
Model 2: Model adjusted for age, sex, and socioeconomic status.
Model 3: Model adjusted for age, sex, socioeconomic status, and affective symptoms measured by the total score of the 12-item General Health Questionnaire (GHQ-12).
We set a random effect of school for the intercept of all models. For Model 3, we added another random effect of school for calculating the slope of the GHQ-12 score.
Missing data (absent = 200, incomplete answers = 71) were excluded from statistical analysis. Analyzable responses were provided by 3040 students (valid response rate: 91.8%).
B, beta coefficients.
Bold means main predictor.

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this limitation by using a large semi-individual level dataset. By using a large data set, we confirmed the significant association between lithium levels in drinking water and psychotic experiences in the general adolescent population. The phenotype of psychotic experiences is not considered a clinical outcome; however, it may share an etiological background with psychotic disorders (Kelleher et al., 2013; van Os et al., 2009). The phenotype we analyzed has the important advantage of not being dependent on help-seeking and is hence suitable for epidemiological research in a representative population-based context (Fusar-Poli et al., 2014). Our results imply that promoting the intake of lithium-rich water could be a potential public health strategy to prevent psychotic symptoms, especially those causing distress and particularly during adolescence, when the risk of psychosis onset reaches its peak, provided no adverse effects are observed in further studies.

We also found that lithium levels in tap water remained significantly associated with psychotic experiences, even after adjusting for the effects of depressive symptoms and confounders (Ando et al., 2017; Nishida et al., 2008; Kelleher et al., 2012a, 2012b). This implies a direct association between lithium in drinking water and psychotic experiences among adolescents, independent of depressive symptoms. Psychotic symptoms are very common in bipolar disorder and about half of the manic episodes comorbid with psychotic symptoms (Coryell et al., 2001; Keck Jr et al., 2003). Lithium is the first-line agent in the treatment of bipolar disorder (Yatham et al., 2009), and clinical studies have reported the antipsychotic efficacy of lithium monotherapy in acute mania (Bowden et al., 2005; de Sousa et al., 2012). However, the antipsychotic effect of lithium for psychotic symptoms in general population was unclear. Our result suggested that lithium in drinking water might have preventive effect for psychotic symptoms in general population.

The biological mechanisms underlying the effect of lithium on psychotic experiences are unclear. Lithium is known to be neuroprotective, by modulating a large array of intracellular cascades and pathways involved in oxidative stress, mitochondrial dysfunction, membrane homeostasis, and inflammation (Manji et al., 2000; Morris and Berk, 2016; Phiel et al., 2003). A recent population-based longitudinal study reported that higher levels of systemic inflammatory markers in childhood were associated with increased risk of developing psychosis in young adulthood, implying that inflammatory pathways might provide novel intervention and prevention targets for such disorders (Khandaker et al., 2014). Future longitudinal population-based studies elucidating the biological effects of long-term micro-doses of lithium on systemic inflammatory markers and onset of psychosis are needed.

The generalizability of our results is likely to be high because the response rate was very high in this study. Nonetheless, this study has several limitations. First, we did not obtain any data on lithium intake from food, which generally exceeds that from drinking water (Schrauzer, 2002). Second, we did not collect data on the use of bottled water, which possibly contains more lithium than tap water. However, Japanese people predominantly drink tap rather than bottled water (Huthwaite and Stanley, 2010); hence, data from tap water might be more relevant. Third, we did not collect information on the total daily amount of tap water consumption, which would moderate the relationship between exposure and outcome. Fourth, the exposure variable (lithium concentration) is still an ecological level variable and, as such, can be misclassified. Fifth, as this study was conducted using a cross-sectional design, we cannot conclude the causal relationship between lithium levels in water sources and psychotic experiences. Finally, we assessed psychotic experiences using only four questions. However, these items were previously used in a birth cohort study and found to have high predictive value for the later development of psychosis (Poulton et al., 2000). In our study, 16.4% of all subjects met the criteria for psychotic experiences, in accordance with findings from other studies using more extensive psychosis assessments (Henquet et al., 2005; van Os et al., 2000).

5. Conclusions

We found that lithium levels in tap water are inversely associated with psychotic experiences and distress among a general population of adolescents. Although further studies are required to examine any adverse effects, we think that the intake of lithium-rich water could constitute a potential public health strategy in preventing psychotic symptoms, especially distressing ones. This strategy would be efficient during adolescence, when the risk of onset of psychosis reaches its peak.

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Contributors

AN, YO, and SS designed the study and wrote the protocol. KS, NO, MM, YY, and KE managed the literature searches and analyses. SK, SA, YI, and SY undertook the statistical analysis, and SS, RF, SK, and AN wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of interest

None declared.

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