Journal of Affective Disorders 298 (2022) 516–521

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Association between lithium levels in drinking water and suicide rates: Role of affective disorders

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ARTICLE INFO

The authors are grateful to the Laboratory UAB Vandens tyrimai for analysis of lithium concentration in drinking water and valuable contribution into this research.

Keywords:
Lithium
Drinking water
Affective disorders
Suicide

ABSTRACT

Objective. The study aimed to assess the association between lithium levels in drinking water from public supplies and suicide rates in different municipalities of Lithuania in relation with incidence of affective disorders.

Methods. 53 drinking water samples were analysed from the main public drinking water systems of the country's municipalities. Lithium levels were determined using the ion chromatography method. Information on all registered affective disorders across all age groups and gender within the 5-year period was obtained from the Department of Statistics, and was averaged across the investigation time period. For the statistical analysis, lithium levels were averaged per municipality and plotted against suicide standardized mortality rates per 100,000 populations, within the 5-year period.

Results. We found that lithium levels in drinking water are positively associated with the incidence of affective disorders. Our findings suggest higher incidence rates of affective disorders in the municipalities with a lithium level in drinking water above median compared to those in the municipalities with a lithium level below median and with the same socio-demographic and psychiatric characteristics. Suicide mortality rates are inversely associated with lithium levels in drinking water only in municipalities with higher lithium levels (above median) and with a high rate of affective disorders.

Conclusion. Based on our study results and insights we generate the following hypothesis for the further research, that lithium level in drinking water might have an important protective effect against suicide rates in the population with affective disorders.

1. Introduction

Although suicide rate around the world declined over the past few years, the overall number of people taking their own lives remains rather high (World Health Organization, 2020). Findings from number of countries, including the United States, has demonstrated a link between higher lithium levels in drinking water and lower rates of suicide in clinical and general populations (Rybakowski, 2020). A study by Ohgami and colleagues demonstrated that even minuscule levels of lithium that present in municipal drinking water could lower that community's risk of suicide (Ohgami et al., 2009). It is an intriguing association, but not all articles demonstrate this association and the exposure to lithium via drinking water is much, much lower than the exposure from lithium therapy (Barjasteh-Askari et al., 2020).

Since the 1960s, lithium has been a precursor of mood stabilizers and has become first-choice drug for the prevention of affective episodes in mood disorders (Geddes et al., 2004; Severus et al., 2014). Lithium has demonstrated possibly specific antisuicidal effects: it significantly reduces the high excess overall mortality of patients with affective disorders. Angst with colleagues found that patients who were treated with lithium, antipsychotics, or antidepressants had a lower suicide rate than those who were not (Angst et al., 2005). Similarly, a UK study showed that at least 40% of patients with bipolar disorder who died by suicide were not prescribed lithium or mood stabilizers (Clements et al., 2013). Also, low-dose lithium has been shown to augment the efficacy of antidepressant medications (Alevizos et al., 2012), enhances

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https://doi.org/10.1016/j.jad.2021.11.045
Received 26 July 2021; Received in revised form 7 October 2021; Accepted 14 November 2021
Available online 17 November 2021

neuroplasticity mechanisms and adult neurogenesis in brain areas such as hippocampus and prefrontal cortex (Girardi et al., 2009; Pompili et al., 2013). For those who are suffering from mood disorders, including treatment-resistant depression, low-dose lithium supplementation may enhance the drug's efficacy as well as reduce the risk of side effects and drug toxicity associated with high-dose lithium treatment.

So, explication of the findings that even the very low levels of lithium provided in drinking water may reduce the risk of suicide is, at present, only speculative (Seidel et al., 2019). Despite this interest, none of the studies, to the best of our knowledge has studied the interaction between the suicide rates, prevalence of mental and behavioral disorders and naturally occurring lithium in drinking water. This is the first study that evaluated the association between lithium levels in drinking water from public supplies and suicide rates in different municipalities of Lithuania in relation with incidence of affective disorders.

In our previous study (Liaugaudaite et al., 2019) we found that lithium intake with drinking water was associated with an incidence of suicide in a nonlinear way (inverted U) and an anti-suicidal effect of lithium in drinking water is present if a lithium concentration is above a certain level. Guided by findings in above cited report our aim was to test the following hypotheses: (1) lithium levels in drinking water are positively associated with the incidence of affective disorders; (2) higher lithium levels in drinking water are inversely associated with the lower suicide rates in areas with high incidence of affective disorders; (3) even very low levels of lithium in drinking water may play a role to save lives among people with affective disorders.

2. Methods

The territory of Lithuania currently comprises 10 counties and 60 municipalities. We selected 54 municipalities, considering the need for homogeneous geographic distribution, covering all regions of the country. For the analyses of lithium concentration in drinking water, we collected groundwater samples in the central wellfields of 54 municipalities, which water supply systems serves the largest percentage of drinking water customers.

2.1. Samples

Fifty-six underwater samples (1 sample per municipality, with one exception – 3 samples in Klaipeda municipality, in which case the results were averaged) from the main public drinking water systems of the country's municipalities were taken during a two-month period (June-July 2017). The underwater samples were collected into special sterile bottles, delivered to the Laboratory for chemical analysis, and stored in the refrigerator until analysis. The Laboratory runs water analysis under the Licence No 983,766 of the Environmental Protection Agency, Republic of Lithuania, issued on 29–10–2012. The lithium concentration in these samples was determined by the ion chromatography DIONEX ICS-1000 (Thermo Scientific, USA) employing the standard LST EN ISO 14,911. Method working range is from 0.01 to 1 mg/l, limit of detection 0.005 mg/l. One underwater sample was excluded from the statistical analyses as a single outlier with a relatively high lithium level (49.0 μg/L) in wellfield. A single outlier was removed from the dataset, and number of 53 water samples were used for further analysis for 53 municipalities out of total 60 municipalities of Lithuania. For the statistical calculations, lithium levels were averaged per district municipality and plotted against suicide standardized mortality rate (SMR) per 100,000 populations.

2.2. Data

Suicide rate data were collected from the Health Information center of the Institute of Hygiene (Lithuania Database of Health Indicators). In accordance with the International Statistical Classification of Diseases (ICD-10) we considered only suicide attempts that resulted in death with the ICD-10 codes from X60 to X84 (Health Information center, 2017). Suicide SMR were age standardized using the European Standard Population measure as defined by the World Health Organization (Waterhouse et al., 1976).

Suicide data comprised all registered suicide events across all age groups and gender within the five-year period (from January 2012 to December 2016). Data on potential confounding factors of suicide risk that included selected municipalities' sociodemographic characteristics such as averaged local population size 2012–2016, unemployment rate (%), number of visits to psychiatrist per 100, divorce rate per 1000 of the population, women/men proportion (number of women per 1000 men), registered any affective disorders (F30-F39), mental and behavioral disorders (MBD) (F00-F99), MBD due to use of alcohol (F10), schizophrenia (F20-F29), diseases of nervous system (G00-G99), attempted suicide, and antidepressant use, across all age groups and gender were obtained from the Department of Statistics, and were averaged across the investigated time period.

2.3. Statistical analysis

Statistical analysis was performed using a statistical software package (SPSS for Windows, version 17.0; IBM-SPSS, Chicago, IL, USA).

A descriptive analysis was conducted to describe the profile of the municipalities. Tests for normality were conducted using a Kolmogorov-Smirnov test and Pearson correlation coefficients or Spearman rank correlation coefficients were calculated between lithium and standardized suicide mortality rates, and among the municipalities routinely collected data. The scatter-plots were used for visualization of relationships between variables. A curve estimation regression analysis was used examining an exponential or quadratic relationship.

The median lithium concentration was calculated (7.0 μg/L) and municipalities with lithium concentration in drinking water greater than the median were assigned to the high lithium exposure group ($n = 26$), the remaining municipalities were assigned to the low lithium exposure group ($n = 27$). Incidence rate of psychiatric disorders and suicide SMR were then calculated according to the median of lithium level. Common statistical techniques multiple linear regression and ANCOVA were used and R-squared was used as the effect size. To investigate whether municipality characteristics had a confounding effect, a multiple linear regression analysis with the suicide SMR (total, men, and women) as the dependent variable was conducted adjusting for mentioned above potential confounding factors of suicide risk. Variance Inflation Factors (VIFs) were investigated. The F-test with $p<0.05$ indicates that the final stepwise or backward regression model is statistically significant. A significance level of alpha <0.05 was used in all analyses.

3. Results

3.1. Analysis according to a median of concentration of lithium in drinking water: low and high lithium exposure groups

The mean lithium concentration in fifty-three drinking water samples was 11.5 (SD 9.9) μg/L ranging from 1.0 to 39.0 μg/L, median – 7.0 (IQR 3.5–20) μg/L.

All analyses were repeated separately for the two groups (low and high lithium exposure groups) categorized to median of lithium level. The descriptive characteristics of the groups are presented in Table 1.

There were no significant differences in sociodemographic characteristics in the municipality between the two groups categorized to median of lithium level. Table 1 indicates that distribution of the affective disorders ($F_{1,51} = 20.26$, $p<0.0001$) and the mental and behavioral disorders ($F_{1,51} = 8.0$, $p = 0.007$) were increased in the high lithium exposure group compared with the low lithium exposure group. The relative difference of incidence of affective disorders was 26.9% and the relative difference of antidepressants use was 19.2% between the low and high lithium exposure groups.

Table 1
Suicide SMR and incidence of mental and behavioral disorders according to the lithium exposure group.

Characteristics per 100,000	Low lithium exposure group $N = 27$	High lithium exposure group $N = 26$	Overall, $n = 53$	F (1,51)	p
Suicide SMRs					
total	42.42±11.27	42.67±11.8	42.54±11.43	0.006	0.938
men	78.37±24.79	79.75±19.54	79.05±22.17	0.05	0.824
women	13.15±4.45	13.41±5.85	13.28±5.13	0.03	0.854
Local populations size 2012–2016	42,176±64,932	36,418±21,224	39,351±48,302		
Median	26,002.3	32,151.1	28,328.9		0.156[a]
Women/1000 men, n	1137.07±49.52	1134.62±46.99	1135.87±47.85	0.34	0.854
Unemployment rate,%	11.18±3.29	11.46±2.56	11.32±2.93	0.13	0.724
Divorces rate per 1000	3.12±0.52	3.26±0.37	3.19±0.46	1.28	0.262
Visits to psychiatrists per 100	26.86±8.49	28.07±7.94	27.46±8.17	0.29	0.594
Incidence of psychiatric disorders					
Mental and behavioral disorders	2553.90±629.84	3246.75±476.91	2893.79±655.72	20.26	<0.001
Affective disorder, total	393.28±189.41	558.71±234.66	474.43±226.68	8.0	0.007
men	205.41±123.64	278.85±141.92	242.13±136.94	4.11	0.048
women	564.64±253.90	783.12±324.99	673.12±309.19	7.57	0.001
Nervous system disease	4364.49±1795.55	4486.37±1289.76	4424.28±1554.20	0.08	0.778
Schizophrenia	44.98±21.90	54.49±24.33	49.65±23.40	2.24	0.141
MBD due to use of alcohol, total	267.12±109.37	306.43±82.84	286.41±98.35	2.16	0.148
MBD due to use of alcohol, men	454.99±193.70	500.57±150.90	477.35±173.89	0.91	0.345
MBD due to use of alcohol, women	98.49±42.16	134.18±41.79	116.00±45.31	9.57	0.003
Antidepressant use per 1000[b]	17.89±8.61	22.14±7.42	19.97±8.30	3.64	**0.062**

Data presented as mean±SD; SD, standard deviation.
SMRs – standardized mortality rate for suicide per 100 000 (European standard population),.
MBD, mental and behavioral disorders.
[a] Mann-Whitney test.
[b] number of the Defined Daily Dose /1000 inhabitants/day.

Antidepressants usage tended to be higher in high lithium exposure group compared with the low lithium exposure group (22.14 ± 7.42 and 17.89±8.61; $F_{1,51} = 3.64$, $p = 0.062$) (Table 1). In the high lithium exposure group, the antidepressants usage rate was significantly positive correlated with lithium levels in drinking water (Spearman' $r = 0.310$, $p = 0.024$), with incidence of MBD ($r = 0.531$, $p<0.001$), affective disorders ($r = 0.596$ $p<0.001$) and MBD due to use of alcohol ($r = 0.374$, $p = 0.006$) (data not shown).

In addition, an increased incidence of MBD due to use of alcohol in women was found in the high lithium exposure group compared with the low lithium exposure group ($F_{1,51} = 9.57$, $p = 0.003$). The incidence of diseases of the nervous system and schizophrenia did not differ between the lithium exposure groups (Table 1).

In Figs. 1 and 2 presented scatterplots of association between lithium and incidence of affective disorder and suicide SMR for both lithium exposure groups. According to Fig. 1 (at right), the fit line approaches a plateau (with a slight increase) in incidence of affective disorders in municipalities with lithium level higher than median (7.0 μg/L).

The results suggest a higher incidence of affective disorders in municipalities above median of lithium level in drinking water compared with other municipalities with the same socio-demographic and psychiatric characteristics. In these municipalities suicide SMR was inversely associated with lithium level in drinking water (Fig. 2, at right). Higher lithium levels might have an important protective effect against suicide mortality particularly in populations with relatively high prevalence of affective disorders.

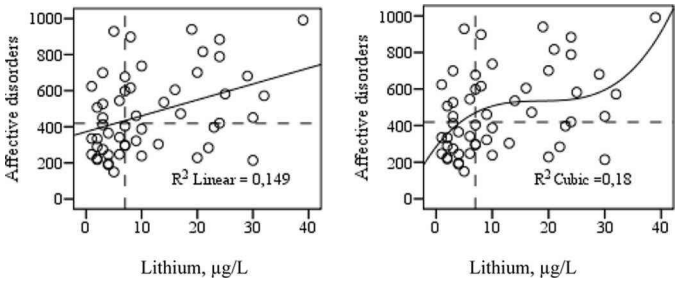

Fig. 1. The fit line for association of affective disorders incidence and lithium, linear (left, $p = 0.004$) and cubic (right, $p = 0.020$). The dash lines indicate: horizontal - a median of the total affective disorders incidence 419/100 000, vertical–median of lithium 7 μg/L.

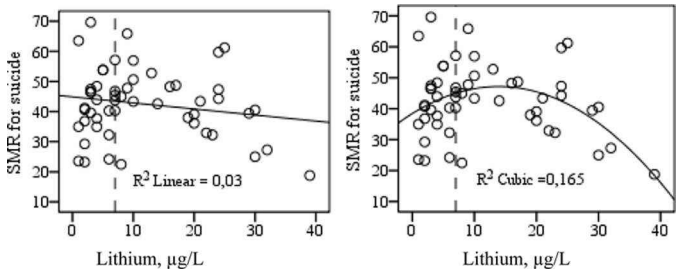

Fig. 2. The fit line for association of total SMR for suicide and lithium, linear (left, $p = 0.212$) and cubic (right, $p = 0.030$) Dash line indicate median of the lithium level in drinking water 7 μg/L.

3.2. Low lithium exposure group: multiple regression analysis of lithium predicting suicide SMRs

We found that the lithium level in drinking water was not associated with suicide SMR in the low lithium exposure group. However, a positive correlation between lithium level and incidence of MBD due to use of alcohol for total, men and women there was found. The incidence of MBD due to use of alcohol (for total, men and women) had a positive correlation with incidence of MBDs ($r = 0.49$, $p<0.01$; $r = 0.48$, $p<0.05$; $r = 0.48$, $p<0.05$ respectively). Incidence of MBDs were more strongly associated with incidence of affective disorders ($r = 0.71$, $p<0.01$) than with incidence diseases of the nervous system ($r = 0.39$, $p<0.05$).

There was no significant association between the lithium levels and the total suicide SMRs in the crude model ($\beta = 0.141$, $t = 0.713$, $p = 0.482$). After adjusting for the relevant factors using a stepwise method, the model could predict total suicide SMRs with statistical significance ($F = 13.42$, $p<0.001$). However, the lithium level was not a significant contributor to the suicide SMR. Among the relevant factors, only the unemployment rate ($\beta = 0.494$, $t = 3.241$, $p = 0.003$) and the incidence

of affective disorders (β = 0.372, t = 2.442, p = 0.022) were significant contributors. Those variables explained over half (R^2 = 52.8%, p<0.001) of variation in total suicide SMR in the low lithium exposure group (Table 2).

In the low lithium exposure group, multiple linear regression revealed the significant and positive associations between unemployment rate (β = 0.439, t = 2.748, p = 0.011) and incidence of mental disorders (β=0.397, t = 2.489, p = 0.020) and suicide SMRs among men (R^2 = 0.498, p>0.001), as well as number of visits to a psychiatrist (β = 0.416, t = 2.846, p = 0.009) and incidence of affective disorder (β = 0.503, t = 3.443, p = 0.002) and suicide SMRs among women (R^2 = 0.509, p<0.001) (data not shown).

3.3. High lithium exposure group: multiple regression analysis of lithium predicting suicide SMRs

Table 3 demonstrate the results of the multiple linear regression analysis of the suicide SMR for the total, women and men in the high lithium exposure group. In the high lithium exposure group there was no association between antidepressant prescribing and suicide SMR, but there was association between antidepressant prescribing and lithium level (r = 0.29, p = 0.035).

In unadjusted crude model, the result reveals a negative and significant association of the total suicide SMR with lithium (β = –0.462, t = –2.555, p = 0.017; R^2 = 0.462) in the high lithium exposure group.

In adjusted model, negative association with lithium remained (β = –0.363, t = –2.135, p = 0.044). Furthermore, a positive association is identified between total suicide SMR and unemployment rate (β = 0.413, t = 2.433, p = 0.023). Those variables explained over third (R^2 = 37.5%, p = 0.005) of variation in total suicide SMR in the high lithium exposure group. In this model, the maximum value of VIF was 1.252, which did not exceed 5, and the minimum value of tolerance was 0.942 indicating no multicollinearity (Table 3).

In unadjusted crude model the results revealed that lithium level was not significant predictors of women suicide SMR (β = –0.343, t = –1.787, p = 0.087). However, after adjustment for sociodemographic characteristic and the incidence of MBD of the municipalities, the result revealed that lithium level (β = –0.455, t = –2.855, p = 0.015), incidence of disease of the nervous system (β = –0.560, t = –2.993, p = 0.007) and incidence of schizophrenia (β = 0.5, t = 2.767, p = 0.011), were significant predictors of women suicide SMR (R^2 = 0.423, p = 0.006). In this model, the maximum value of VIF was 1.322, which did not exceed 5, and the minimum value of tolerance was 0.751 indicating no multicollinearity.

Table 2
Multiple regression analysis of lithium predicting suicide SMRs in the low lithium exposure group (N = 27).

	Coefficients				
	Unstandardized		Standardized		
Variables	B	SE	Beta	t	p
SMR total					
Crude model					
(Constant)	39.37	4.81		8.18	<0.001
Lithium, μg/L	0.189	1.08	0.141	0.713	0.482
Model: F = 0.029, p = 0.867, R^2=0.001					
Adjusted model[a]					
(Constant)	6.112	5.981		1.022	0.317
Unemployment rate,%	1.969	0.608	0.494	3.241	0.003
Affective disorders	0.029	0.012	0.372	2.442	0.022
Model: F = 13.42 p<0.001, R^2=0.528					

SE, standard error;.

[a] adjusted for sociodemographic characteristics of the municipalities and following adjustment for the incidence of the MBD Sociodemographic characteristics of the municipalities: local population size, women/1000 men, unemployment rate, divorce rate, visits to psychiatrists per 100. Mental and behavioral disorders (MBD): affective disorders, MBD for men, MBD for women, diseases of nervous system, schizophrenia.

There was a crude negative association between SMR for men suicide and lithium level (β = –0.452, t = –2.484, p = 0.020; R^2 = 0.204). Adjusting for sociodemographic covariates did not impact the association between SMR for men suicide and lithium level, but adding incidence of the MBD to the final model further reinforce this association (β = –0.465, t = –2.855, p = 0.009). In addition, result reveals that suicide SMR among men may be higher in municipality with higher incidence of MBD due to use of alcohol for women (β = 0.433, t = 2.659, p = 0.014) (Table 3).

4. Discussion

The current study suggests that incidence of affective disorders was higher in municipalities with high lithium exposure (lithium level above median >7 μg/L). The relative difference of incidence of affective disorders was 26.9% and antidepressants use tended to be higher in high lithium exposure group by 19.2%.

This is the first study to investigate the relationship between suicide SMR, lithium levels in drinking water, sociodemographic characteristics and incidence of MBDs simultaneously. So far, no studies have been found that focused on an association of lithium in drinking water with the incidence of affective disorders in the study region.

No recent studies have been found that analyze the association of lithium level in drinking water with the incidence of mental and behavioral disorders in Eastern Europe. This is the first report to investigate the relationship between suicide SMRs, lithium levels in drinking water, socio-demographic characteristics and incidence of affective disorders in multiple municipalities simultaneously.

For the first time, in our previous studies (Liaugaudaite et al., 2017, 2019) we found that lithium intake with drinking water was associated with an incidence of suicide in a nonlinear way (inverted U) and an anti-suicidal effect of lithium in drinking water is not present if a lithium concentration is below a certain level.

Our study suggests that incidence of affective disorders was higher in municipalities with high lithium exposure (lithium level above median >7 μg/L). In municipalities with above median of lithium level, suicide SMR for total population and among men and women was inversely associated with lithium level in drinking water. Higher lithium levels might have an important protective effect against suicide mortality particularly in populations with relatively high prevalence of affective disorders. Therefore, individuals with affective disorders may be more sensitive to the anti-suicidal effect of lithium.

This suggests that long term exposure to lithium in drinking water in high lithium exposure areas may have specific anti-suicidal effects in suicide-survivals and those with affective disorders, which in the end may increase the number of individuals with affective disorders in high lithium exposure areas. In addition, multiple regression analysis revealed strong negative association between suicide SMR (total, women and men) and lithium level over median (7 μg/L) controlling for municipalities' characteristics and incidence of mental and behavioral disorders.

Unlike most international studies regarding natural lithium levels and suicide risk, no inverse relation was found of four studies (Kabacs et al., 2011; Pompilli et al., 2015; Oliveira et al., 2019; Kozaka et al., 2020). In these studies, potential confounding factors were sociodemographic data. Factors such as the country's low suicide rate, confounding suicide risk variables, psychiatric disorder, and unaccounted lithium intake might have influenced these findings.

A proportion of patients with affective disorder does not get treatment, a proportion may have been treated with poor response to lithium prior to the study period, and a proportion may have been treated with mood stabilizers other than lithium and/or other medications. We are not aware of other national prescribed lithium prevalence rates besides that in Germany, where lithium salts are in frequently prescribed within the National Health Scheme (specifically, to 0.06% of the population) (Ahrens and Müller-Oerlinghausen, 2001, 2003; Müller-Oerlinghausen

Table 3
Multiple regression analysis of lithium predicting suicide SMRs in the high lithium exposure group ($N = 26$).

Dependent variable		Coefficients				
		Unstandardized		Standardized		
	Model	B	SE	Beta	t	p
Total suicide SMR	Crude model					
	(Constant)	55.181	5.325		10.363	<0.001
	Lithium, μg/L	**−0.643**	**0.252**	**−0.462**	**−2.555**	**0.017**
	Model: R^2=0.462; $F = 6.529$, $p = 0.017$					
	Adjusted model[a]					
	(Constant)	30.679	11.178		2.745	0.012
	Lithium, μg/L	**−0.504**	**0.236**	**−0.363**	**−2.135**	**0.044**
	Unemployment rate,%	1.901	0.781	0.413	2.433	0.023
	Model: R^2=0.375, $F = 6.894$, $p = 0.005$					
Women suicide SMR	Crude model					
	(Constant)	18.008	2.795		6.444	<0.001
	Lithium, μg/L	**−0.236**	**0.132**	**−0.343**	**−1.787**	**0.087**
	Model: R^2=0.117, $F = 3.194$, $p = 0.087$					
	Adjusted model[a]					
	(Constant)	24.215	4.744		5.104	<0.001
	Lithium, μg/L	**−0.306**	**0.116**	**−0.455**	**−2.637**	**0.015**
	Nervous system disease	−0.003	0.001	−0.560	−2.993	0.007
	Schizophrenia	0.120	0.043	0.500	2.767	0.011
	Model: R^2=0.423, $F = 5.369$, $p = 0.006$					
Men suicide SMR	Crude model					
	(Constant)	99.988	8.863		11.281	<0.001
	Lithium, μg/L	**−1.040**	**0.419**	**−0.452**	**−2.484**	**0.020**
	Model: R^2=0.204, $F = 6.168$, $p = 0.020$					
	Adjusted model[a]					
	(Constant)	73.394	12.758		5.753	<0.001
	Lithium, μg/L	**−1.068**	**0.374**	**−0.465**	**−2.855**	**0.009**
	MBD due to use of alcohol, women	0.202	0.076	0.433	2.659	0.014
	Model: R^2=0.391, $F = 7.398$, $p = 0.003$					

SE, standard error;.

[a] adjusted for sociodemographic characteristic of the municipalities (local population size, women/1000 men, unemployment rate, divorce rate, visits to psychiatrists per 100) and following adjustment for the incidence of the MBD: affective disorders, MBD due to use of alcohol, MBD due to use of alcohol women, MBD due to use of alcohol men, diseases of nervous system, schizophrenia.

et al., 2003).

The mechanism by which lithium may reduce suicides is hypothesized to be the reduction of impulsive and aggressive behavior in bipolar and depressed patients. Some authors suggest, it is thought to have a specific anti-suicide effect exceeding its mood stabilizing properties (Volkmann et al., 2020; Ahrens and Müller-Oerlinghausen, 2001). On the other hand, although lithium levels are extremely low in drinking water, long-term exposure to lithium may be a factor which mitigates low absolute levels. It can be speculated that very low but very long lithium exposure can enhance neurotrophic factors, neuroprotective factors and/or neurogenesis, which may account for a reduced risk of suicide (Müller-Oerlinghausen, 2007).

Some researchers have even theorized that adding lithium to drinking water could potentially reduce the rate of suicide among the general population (Ohgami et al., 2009; Lewitzka et al., 2015). However, the actual concentration needed to induce anti-suicidal effects in people with affective disorders and, possibly, other individuals remains unclear (Steiner et al., 2012).

The findings of our study also raise the interesting possibility that it is likely that in the absence of prescribed lithium in the population for the treatment of affective disorder, lithium in drinking water may have an anti-suicidal effect for those with affective disorder. The study by Lewitzka et al. (2015) also suggests that the expected higher overall mortality in patients with affective disorders using lithium is decreased . Also, lithium reduces impulsivity and aggression, and, consequently, may reduce mortality related to violence or accidents (Giotakos, 2018; Malone et al., 1994; Ohmura et al., 2012).

4.1. Limitations

The main limitation of the present study is due to the nature of observational research which cannot reveal a causal relationship. It should be noted that ecological studies per se are designed to establish hypotheses rather than to provide cause due to immeasurable individual exposures and confounders (ecological fallacy) (Piantadosi, 1988). Thus, although informative, the estimates should be interpreted with caution due to the aggregated nature of data.

Secondly, official data on the registered incidence of mental and behavioral disorders and suicide rates are also relatively uninformative due to their incompleteness and the lack of specific epidemiological surveys. Also, we do not know/cannot take into account people's daily job/living area migration patterns or their tap water consumption tendencies while in different areas. On the other hand, lithium rich food often comes from worldwide market, while drinking water usually has a local origin.

Limitations include the use of cross-sectional data. The present study was based on the correlations among suicide SMR, a relatively limited number of discrete diagnoses of mental and behavioral disorders, and the central public drinking water wellfields of municipalities.

Finally, the use of the term "nonlinear" in this study refers to the relationship, not the statistical model. We discussed how such relationships can be better theorized and tested. The examined model of suicide mortality is subject for further interesting research questions. Since all data were not collected in a prospective fashion, the models developed can only be used to test for an association between these independent variables and the outcome; rather than to identify and determine the risk factors or determinants for suicide SMR.

5. Conclusion

Higher lithium levels in drinking water are significantly and inversely associated with the lower suicide rates in municipalities with high incidence of affective disorders. This suggests that long term exposure to lithium in drinking water in high lithium exposure areas may have anti-suicidal effects on persons with affective disorders, which may reduce suicides and consequently, increase the number of

individuals with affective disorders in high lithium exposure areas.

CRediT authorship contribution statement

Vilma Liaugaudaite: Conceptualization, Writing – original draft, Data curation. **Nijole Raskauskiene:** Methodology, Formal analysis, Data curation. **Rima Naginiene:** Visualization, Writing – review & editing. **Narseta Mickuviene:** Supervision, Writing – original draft. **Leo Sher:** Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Acknowledgments

This research was in part financed by the Research Foundation of the Lithuanian University of Health Sciences.

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