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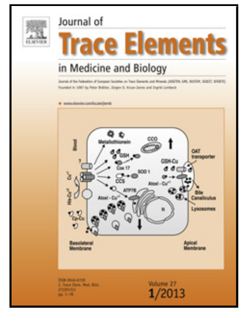

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Title

Lithium levels in the public drinking water supply and risk of suicide: a pilot study

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Highlights

- The suicide-protective property of natural lithium was confirmed with a positive effect for men.
- Higher lithium levels in drinking water might have a protective effect on the risk of suicide in men.
- Evaluation of lithium in a local drinking water, might provide regional effective prevention programs.

Abstract

Suicide is a major public health concern affecting both the society and family life. There are data indicating that higher level lithium intake with drinking water is associated with lower suicide rate. This pilot study examined the relationship between lithium levels in drinking water and suicide rates in Lithuania. Twenty-two samples from public drinking water systems were taken in 9 cities of Lithuania. The lithium concentration in these samples was determined by inductively coupled plasma mass spectrometry (ICP-MS). The suicide data were obtained from the Lithuania Database of Health Indicators, and comprised all registered suicides across all ages and gender within the 5-year period from 2009 to 2013. The study demonstrated an inverse correlation between levels of lithium (log natural transformed), number of women for 1,000 men and standardized mortality rate for suicide among total study population. After adjusting for confounder (the number of women for 1,000 men), the lithium level remained statistically significant in men, but not in women. Our study suggested that higher levels of lithium in public drinking water are associated with lower suicide rates in men. It might have a protective effect on the risk of suicide in men.

Key Words: Lithium; Suicide; Drinking water

1. Introduction

Suicide is a huge public health issue determined by various factors including psychiatric disorders, socio-economic, environmental and other causes [1-13]. The World Health Organization reports that suicide is a major public health concern accounting for approximately 800,000 deaths annually worldwide including approximately 58,000 deaths in the European Union, and 1,000 deaths in Lithuania [14]. Lithuania with population of about 3 million in the beginning of 2014 had the highest suicide rate in the Europe in 2014 – 31.7 cases per 100,000 people [15, 16]. Rates of suicide in many European countries and North America are 2–4 times higher in men than women. Although that female gender is associated with suicide attempts, male gender is associated with suicide deaths [9, 13].

Lithium is naturally found in vegetables, grains and drinking water [17-19]. Nutritional studies suggest that lithium is an essential trace element with a recommended dietary allowance of 1 mg/day [17]. Observational studies in Japan suggest that naturally occurring lithium in drinking water may increase human lifespan [20]. Lithium in therapeutic doses (usually, 600-1800 mg per day) is widely used for treatment of manic and depressive episodes, and it may be associated with reduced rates of suicide and suicide attempts in patients with bipolar disorders [21-23]. A placebo-controlled trial data showed that low doses of lithium might improve and stabilize mood quite rapidly in former drug users [24].

Although natural lithium intake doses are significantly lower than those used for the treatment of patients with psychiatric disorders [25, 26], there is growing evidence that even very low lithium levels induced by routine consumption of lithium from tap water may have anti-suicidal effects both in patients with mood disorders, and in the general population [27, 28]. One of hypotheses explaining anti-suicidal effects of low lithium levels is that long-term exposure to lithium through routinely drinking water may mitigate low absolute lithium levels [18]. Lithium is detectable at variable concentrations in drinking water throughout the world [25, 26, 29, 30]. The findings in different countries provided evidence that higher lithium levels in the public drinking water may be associated with lower suicide rates [2, 18, 27, 29, 31-36]. The hypothesis of our study was that higher natural lithium levels in the public drinking water are associated with lower suicide rates. This is the first study in Eastern Europe investigating the association between lithium levels in public drinking water and suicide rates.

2. Methods

2.1. Suicide data

The suicide data were collected from the Health Information Centre of Institute of Hygiene (Lithuania Database of Health Indicators). In accordance with International Statistical Classification of Diseases (ICD-10) the data included only suicide attempts which resulted in death with codes: X60-X84 [15]. Suicide standardized mortality rates (SMR) were age standardized using the European Standard Population measure as defined by the World Health Organization [37]. Suicide data comprised all registered suicides across all age groups and gender within the period of 5 years, from 2009 to 2013.

2.2. Study area

In 2013 the Lithuania had 2,971,905 inhabitants, 1,367,076 males and 1,604,828 females, respectively. There are 103 cities, 249 towns, and 21,000 villages in Lithuania [16]. We focused on the cities but not on the towns or villages in order to decrease as much as possible the impact of the heterogeneity of economic and cultural background.

These nine cities had the population of 1,190,261 (41% of general population of Lithuania). The average population per studied city was 132,293 (SD 178,161) inhabitants with a range from 2,525 in the Birstonas city to 526,356 in the capital city Vilnius, respectively [16].

2.3. Measurement of lithium levels in public drinking water

During a three-months period (November 2013 – January 2014), 22 samples (range from 1 to 5 per city) of drinking water from public water supply system of nine Lithuanian cities were taken and analyzed for lithium levels by inductively coupled plasma mass spectrometry (ICP-MS) NexION™ 300D (PerkinElmer, USA). The analysis was performed applying standard mode and using argon gas (purity ≥99.996) following the manufacturer's recommendations. The calibration ranged from 0 to 100 µg/L, and was done using Multi-Element Calibration Standard 3 (Pure Plus PerkinElmer, USA). Each single Li result in drinking water sample was an average of 3 repeated analyses, and the SD for the min result was 0.48 µg/L (SD±0.001), and for the max result – 35.53 µg/L (SD±0.866).

Therefore, all laboratory and equipment manipulations were performed in a recommended for ICP-MS analysis Laboratory room environment and operating conditions, and controlled for the possible trace elements and lithium (if any) contamination. The analytical quality control, accuracy and precision of the analysis were ensured by applying internal and external quality control procedures. The analytical balances and pipettes are checked and calibrated, if needed, once a year using Laboratory in-house approved procedures. The purity of reagents and chemicals are controlled on a routine basis while purchasing. Every new purchased lot of labware (containers for the drinking water sampling in this case, laboratory tubes, pipettes disposable tips, etc.,) are checked-up and controlled for the possible trace elements, including lithium, contamination, and decontaminated with 2.4 M nitric acid (≥69.0%, TraceSELECT®, FLUKA) if needed on a routine basis. The lithium detection limit (LoD), using seven replicated spiked with 1.0 µg/L of Multi-Element Calibration Standard 3 (Pure Plus PerkinElmer, USA) was 0.154±0.03 µg/L and derived as described [38]. The lithium mean ±SD of seven replicates was 10.149±0.24 µg/L (min 9.992 µg/L (±0.60), max 10.545 µg/L (±0.168)) as a reference material using 10.0 µg/L Multi-Element Calibration Standard 3 (Pure Plus PerkinElmer, USA), and 11.24±0.34 µg/L (min 10.855 µg/L (±0.04), max 11.875 µg/L (±0.04)) as a reference material using 10.0 µg/L lithium chloride (≥99.99%, trace metal basis, Sigma-Aldrich, Germany). Every reported lithium concentration is an average of 3 repeated analyses and derived following apparatus manufacturer's recommendations.

2.4. Statistical analysis

For the statistical calculations, lithium levels were averaged per city and plotted against suicide SMR per 100,000 people. Data on female/male proportion (number of females per 1000 males) were obtained from the Department of Statistics, and averaged for the investigated 2009-2013 years period [16].

At first, we transformed nonlinear model to a linear model, which can be analyzed using linear regression. Weighted least squares regression analysis, adjusted for the size of population in each city, was used to investigate the association between lithium levels in public drinking water supply and suicide SMRs. When a nonlinear pattern was corrected by a log transformation, it was accompanied by a substantial increase in the value of R^2: from 0.068 ($p=0.248$) to 0.467 ($p=0.025$). If the value of R^2 changed, then the relationship was not linear and the transformation was effective. The log transformation of lithium level reduced the nonlinearity in the relationship, but was less effective than the addition of the polynomial term, both in terms of linearizing the distribution of points on both sides of the fit line and in terms of the increase in R^2. The addition of the logarithmic term, produced reliable results indicating that there is a strong relationship between suicide SMR and lithium levels, when lithium level is represented by a combination of the original variable and the log form of the original variable ($R^2= 0.774$, $p=0.005$).

The association between lithium levels in public drinking water and suicide rates was examined before and after including the proportion of female/male as possible confounding factor in multiple regression models. A value of $p<0.05$ was considered significant. The data were analyzed using SPSS for Windows, version 17.0 (SPSS Inc; Chicago, III., USA).

3. Results

In 2009-2013, total suicide SMR mean was 27 (range 16-50); males – 51 (range 29-93) and females – 7 (range 0-13). For cities (n=9) providing more than one water sample (2.44 samples/city, overall) lithium levels in local drinking water were averaged. Averaged value (nine cities) ranked (mean ± SD, μg/L): 1.24±0.67; 2.91±0.69; 3.89; 5.05±3.91; 5.78±4.05; 6.94±1.69; 13.1±16.9; 21.7 and 28.68±9.68. Overall, lithium level in all 22 samples was 10.9 (SD 9.1) μg/L, ranged from 0.48 to 35.53 μg/L while median level was 3.6 μg/L

The analyses showed nonlinear relationship between suicide SMRs and lithium levels in drinking water. We used the Curve Estimation procedure to identify functional relations between lithium levels and standardized mortality rates of suicide. At first we examined scatterplots that showed the pattern of both variables. The nonlinearity was assessed by including the fit line on the scatterplot (Figure 1).

Table 1 demonstrated an inverse correlation between levels of lithium (log natural transformed), proportion of female/male and SMR for suicide in total study population and in men. These variables did not significantly correlate with the suicide SMR in women.

SMRs for suicide in 9 cities of Lithuania were negatively associated with lithium levels in drinking water (β=–0.91, p=0.001, for both genders). After adjusting for proportion of female/male, the association with lithium level in drinking water remained statistical significant (β=–0.28, p=0.034, for both genders) (Table 2).

SMRs for suicide across the nine cities of Lithuania were negatively associated with log lithium levels in drinking water for men (β=–0.96, p< 0.001), but not with log lithium levels for women (β=0.15, p=0.70). After adjusting for confounder (proportion of female/male), the association was significant only for men (β=–0.70, p=0.013) (Table 3).

The study demonstrated an inverse correlation between levels of lithium (log natural transformed), proportion of female/male and SMR for suicide among total study population. After adjusting for the confounder (proportion of female/male), the lithium level remained statistically significant in men (β=–0.70, p=0.013), but not in women (β=0.15, p=0.70).

4. Discussion

This is the first study in Eastern Europe investigating the association between natural lithium levels in the public drinking water and suicide rates. The present study tested the hypothesis whether higher natural lithium levels in the public drinking water were associated with lower local suicide rate in 9 cities of Lithuania. Overall, the findings support an inverse relationship of lithium levels and suicide rate in men.

The natural lithium levels in drinking water have correlated inversely with suicide risk in most [17, 18, 31, 35, 39], but not in all studies of the relationships between lithium levels in drinking water and suicide rates [29, 36].

In Lithuania, men suicide rate is 6 times higher than women [15]. This is consistent with recently published meta-analyses indicating that female gender is associated with suicide attempts, while male gender is associated with suicide deaths [9, 40]. Probably, men are more likely to complete suicide attempts because they choose more violent means of death [3, 13, 41, 42]. These gender differences may be explained by the fact that natural lithium intake may influence impulsiveness, a factor that contributes to suicidal behavior [43-45] and that men respond better to lithium treatment than women [24].

Our results are consistent with previous studies that lithium in drinking water was negatively associated with suicide in men [2, 31, 32, 35, 41]. For example, a large number of samples of drinking water were examined in relation to suicide standardized mortality ratios (SMRs) in about 300 municipalities in Japan [35]. The authors found that lithium levels in drinking water were significantly and inversely associated with male suicide SMRs but not total or female SMRs. This implies that suicide prevention strategies and programs must reflect gender dissimilarities and local circumstances in risk patterns by providing specific localized health intervention strategies, such as reducing suicide risk factors and improving protective factors related to mental health and well-being.

Understanding the mechanism by which lithium acts to decrease suicidal behavior could lead to a better understanding of the neurobiology of suicide in men [46]. Treatment of patients with suicidal behavior is one of the most challenging tasks for health-care professionals [1, 42, 47]. The evaluation of risk factors associated with suicidal behavior, e.g. lithium in a local drinking water, might provide regional effective prevention programs.

Our study results also indicate that suicide risk varied considerably across the 9 cities of Lithuania, based on multivariate modeling that was considering local population size, and comprehensive data on female/male proportion. A recently published review supports the association between higher lithium levels in drinking water and reduced risk of suicide in the general population [27].

Dietary intakes of lithium are approximately 0.5-3 mg daily and naturally occurring serum lithium concentrations in adults are typically 7-28 μg/L [17], some are nearly zero [48]. Drinking water is not the only dietary source of lithium. Vegetable and grains are the important dietary sources of lithium and account for two-thirds of lithium intake, whereas drinking water comprises the remaining third [48]. Unfortunately, we could not find the data of lithium concentrations in foodstuff of Lithuanian market.

Although lithium concentrations in ground water varies between <0.05 to 150 μg/L, the reports from the Austria, the northern Chile, and the northern Argentina have showed very high lithium concentrations in drinking water (over 1000 μg/L) [2, 49, 50]. Other research shows that in temperate humid zones the lithium levels in ground water are lower than in dry, hot regions (about 1500 μg/L) [51]. There are not drinking water standards for lithium in the European Union. Although, the median value of lithium was evaluated in European bottled waters (9.94 μg/L), we could not find the data of lithium concentrations in drinking water of the other Baltic or neighborhood countries [52].

Only individuals who died as a result of their suicide attempts, i.e., suicide completers were included in our study. Although suicide attempters who did not die by suicide and suicide completers are overlapping groups of troubled individuals, studies suggest that there are differences in demographic and clinical features and behavior between these two groups [53-55]. Therefore, it is possible that if we would study a relation between suicide attempters who did not die by suicide and lithium levels in the drinking water the results could have been different.

Our study has some limitations. First, the present findings are derived from the nine cities of Lithuania (41 percent of the general population), and thus only limited generalization is possible. Second, dietary sources of lithium uptake include bottled water [34], vegetables, grains, and spices [27, 35]. Also, we do not know/cannot take into account people's daily job/living area migration patterns and their tap water consumption tendencies while in one or another area. On the other hand, lithium rich food often comes from worldwide market and different countries, while drinking water usually has the local origin.

Third, other factors such as psychosocial and economic factors, as well as religious affiliations, were not taken into consideration. We could not obtain data how many of those suicide committed people actually had (and how long it took) the lithium treatment, and which person had psychiatric illness. Thus, the finding for association of lithium in drinking water and suicide mortality rate could be biased by possible lithium treatment (if any) and therefore not solely affected by natural lithium occurrence.

5. Conclusions

The suicide-protective property of natural lithium was confirmed with a positive effect for males. Our study suggests that higher lithium levels in the public drinking water might have a protective effect on the risk of suicide among men. The findings of this pilot study needs to be treated with caution until replicated. It is also important to assess whether lithium levels in the public drinking water supply correlate with blood lithium levels.

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Conflict of interest

There are no conflicts of interest.

Role of the founding source

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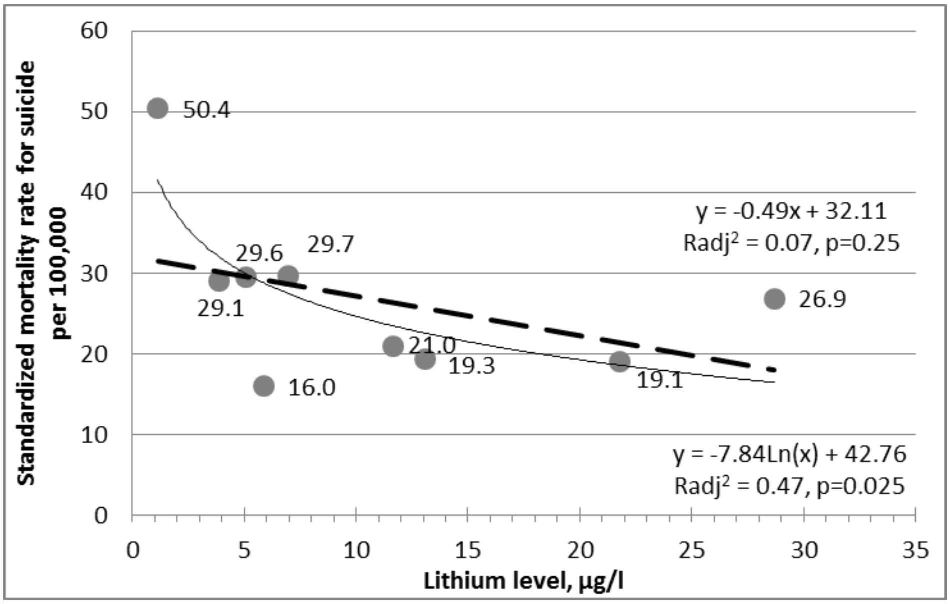

Figure 1. Lithium levels in drinking water and the average suicide standardized mortality rate for 5 years (2009-2013) in 9 cities of Lithuania. Dotted line refers to a linear regression and solid line to a polynomial regression.

Table 1. Pearson correlation coefficient (r) between standardized mortality rate for suicide (2009-2013) and cities characteristics.

Cities characteristic	Standardized mortality rate for suicide (per 100,000)		
	Total	Men	Women
Lithium level, mean (µg/l)	–0.430	–0.016	–0.448
Log lithium level, mean[a]	–0.731*	–0.728*	–0.276
Female/male proportion[b]	–0.770*	–0.726*	-0.488

[a] logged lithium level in drinking water

[b] number of women for 1,000 men

[*] $p<0.05$

Table 2. Regression models weighted for size of each population on standardized mortality rate for suicide.

	Association with standardized mortality rate for suicide		
	β	t value	p
Model 1			
Lithium level	0.560	1.789	0.117
Model 2			
Log lithium level[a]	–0.911	–5.841	0.001
Model 3			
Log lithium level[a]	–0.283	–2.886	**0.034**
Female/male proportion[b]	–0.713	–7.319	0.001

[a] logged lithium level in drinking water

[b] number of women for 1,000 men

Table 3. Regression models weighted for size of each population on standardized mortality rate for suicide according to gender.

	Association with standardized mortality rate for suicide					
	Men			Women		
	β	t value	p		value	
Model 2						
Log lithium level[a]	–0.965	-9.684	**<0.001**	0.150	0.402	0.700
Model 3						
Log lithium level[a]	–0.702	–3.515	**0.013**	0.253	0.677	0.523
Female/male proportion[b]	–0.296	–1.484	0.188	0.490	1.311	0.238

[a] logged lithium level in drinking water

[b] number of women for 1,000 men