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# Investigation of the association between lithium levels in drinking water and suicide mortality in Hungary

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A R T I C L E I N F O

*Keywords:*
Lithium
Drinking water
Suicide
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A B S T R A C T

*Background:* In recent decades, a series of ecological studies from various countries have attempted to reveal whether there is an association between trace amounts of lithium in drinking water and suicide mortality. With some notable exceptions, results have indicated that there is an inverse association between these two variables. Since Hungary had extremely high rates of suicide with a persistent spatial pattern, we consider that our country is ideal to investigate this research question.
*Methods:* We carried out our research on Hungarian data at the level of districts ($n$ = 197). The dependent variable was the age- and gender-standardized mortality ratio for suicide (***sSMR***). Our main explanatory variable was the tap water lithium level (***Li***) from public drinking water supply systems using their own water source ($n$ = 1 325). Those data, which give full national coverage, were aggregated to the level of districts. Confounding factors were religiosity, alcohol consumption and income. Various regression models were used for statistical calculations.
*Results:* Findings from our most appropriate regression model – adjusted for relevant confounding variables and able to handle spatial autocorrelation and heteroscedasticity – suggest a significant ($p < 0.05$) and a trend-like ($p < 0.1$) negative association between ***Li*** and ***sSMR*** in the total population and among males, respectively. However, such an association was not found between these two variables among females.
*Conclusion:* In line with the majority of findings from other countries, our results indicate that the intake of lithium with drinking water may have a gender-dependent suicide-protective effect.

## 1. Introduction

Suicide is a major public health issue, with about 800,000 death cases per year globally. This figure makes suicide one of the twenty leading causes of death. In 2016, global suicide rates (/100 000) for total population, males and females were 10.5, 13.7 and 7.5, respectively (World_Health_Organization, 2019; https://www.who.int/teams/mental-health-and-substance-use/suicide-data). In young people (aged 15–29) suicide is the second leading cause of death (World_Health_Organization, 2019). Suicidal behavior has several known risk factors, including medical issues (primarily psychiatric conditions [e.g. major depressive disorder], substance use and severe somatic disorders, previous suicidality), personality/cognitive characteristics (e.g. impulsivity/hostility, hopelessness, perfectionism, thwarted belongingness, perceived burdensomeness), as well as demographic and socioeconomic factors (e.g. male gender, older age, low educational attainment, unmarried status), negative/stressful life-events (e.g. becoming unemployed, experiencing bullying/cyberbullying), belonging to sexual minorities (i.e. homosexuality and bisexuality) and genetic susceptibility (Balint et al., 2014; Bálint et al., 2016; Del Matto et al., 2020;

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Holman and Williams, 2020; McClatchey et al., 2017; O'Connor and Nock, 2014; Rihmer, 2007; Schreiber and Culpepper, 2020). There are also known protective factors with regard to suicidal behavior such as social support/sense of belonging, resilience and religiosity (especially in Western cultures) (Balint et al., 2014; Holman and Williams, 2020; Jacob et al., 2019).

Lithium has been used for the treatment of various medical conditions from the mid-1800s. Although over time the use of lithium has become obsolete in its somatic "indications" (e.g. gout and cardiac disorders), it has remained a mainstay in therapy for mood disorders, for which it began to be used in the 1950s (Baldessarini, 2013; Hidvégi et al., 2016; Mitchell, 2001). More specifically, lithium has a phase-prophylactic and antimanic effect in bipolar disorder. Furthermore, lithium is also effective as an augmentation to antidepressants, as well as being effective in the prevention of recurrence of depressive episodes in major depressive disorder (Barroilhet and Ghaemi, 2020; Gitlin, 2020; Hidvégi et al., 2016; McIntyre et al., 2020). Finally, according to the results of double-blind RCTs and their meta-analyses, lithium treatment is able to prevent suicides in subjects with mood disorders (Barroilhet and Ghaemi, 2020; Del Matto et al., 2020; Hidvégi et al., 2016; Memon et al., 2020; Smith and Cipriani, 2017). The observation that lithium may have an antisuicidal effect even among individuals with mood disorders who are (partially) non-responsive to its mood-stabilizing properties suggests that there should also be other explanations for this effect. Such alternative explanations may be related to lithium's role in reducing aggression and impulsivity (Ahrens and Müller-Oerlinghausen, 2001; Barjasteh-Askari et al., 2020; Del Matto et al., 2020; Hidvégi et al., 2016; Memon et al., 2020). In addition to clinical trials, from the 1970s several ecological studies have investigated the possible relationship between trace amounts of lithium in drinking water and the suicide risk of the population (it is worth mentioning that lithium exposure from drinking tap water is several orders of magnitude less than the therapeutic dose of lithium) (Dawson et al., 1972; Hidvégi et al., 2016; Kapusta et al., 2011; Liaugaudaite et al., 2019; Schrauzer and Shrestha, 1990). With a few notable exceptions (e.g. Kabacs et al., 2011; Knudsen et al., 2017; Oliveira et al., 2019), the majority of these studies suggest that higher lithium intake from tap water is associated with lower risks for suicide at the population level. In the last year, three meta-analyses of these ecological studies have also been published, all of which came to the conclusion that higher amounts of lithium in drinking water are associated with reduced suicide risks in the population (Barjasteh-Askari et al., 2020; Eyre-Watt et al., 2021; Memon et al., 2020). Intriguingly, however, it seems that the protective effect of lithium may be more pronounced among men than among women (Barjasteh-Askari et al., 2020; Del Matto et al., 2020), though the results of ecological studies and their meta-analyses are not entirely conclusive in this regard (see, for instance, Memon et al., 2020; Sugawara et al., 2013). Furthermore, results of some ecological studies also suggest that the suicide-protective effect of lithium has a concentration threshold (i.e. it appears only above a given lithium concentration in the drinking water) (Kugimiya et al., 2021). In line with the results of the aforementioned ecological studies suggesting that even trace amounts of lithium may have suicide-preventive effects, a study from Japan found significantly lower serum lithium levels in suicide attempters than in control subjects (all participants were lithium therapy-naïve). Similar to the results of most ecological studies, findings of that investigation indicate that the suicide-protective effect of lithium is limited to males (Kanehisa et al., 2017). A few placebo-controlled clinical investigations have also supported the conjecture that lithium is bioactive even in very low doses. Accordingly, lithium administration at the level of 100 μg/day may have beneficial impacts on the progression of cognitive decline in patients with Alzheimer's disease and improved "happiness", "friendliness" and "energy" in former drug user subjects (Nunes et al., 2013; Schrauzer and de Vroey, 1994). Finally, the plausibility of the bioactivity of microdose lithium is also supported by some epidemiological studies where the investigated outcome was not suicide. For instance, a Danish study found that tap water lithium levels were inversely associated with the incidence of dementia (though the association was non-linear) (Eyre-Watt et al., 2021; Kessing et al., 2017a). Furthermore, results of another study from Japan suggested a similar inverse relationship with psychotic experiences among adolescents (Eyre-Watt et al., 2021; Shimodera et al., 2018). In addition, the same research group found that tap water lithium levels were inversely associated with depressive symptoms and interpersonal violence in the same adolescent sample (Ando et al., 2017; Eyre-Watt et al., 2021). Furthermore, a meta-analysis found a negative association between tap water lithium levels and the number of psychiatric admissions (Eyre-Watt et al., 2021). By contrast, a study from the USA was unable to demonstrate such associations for bipolar disorder, dementia and major depression (Eyre-Watt et al., 2021; Parker et al., 2018). Similarly, a study from Denmark did not find a significant association between higher lithium exposure from drinking water and lower incidence of bipolar disorder (Eyre-Watt et al., 2021; Kessing et al., 2017b). Finally, another Danish study found no relationship between lithium levels in drinking water and the risk of incident bipolar disorder. Hence they found a *positive* association between lithium levels and incident schizophrenia and schizophrenia spectrum disorders (Schullehner et al., 2019). Given the almost unambiguous results on the inverse association between tap water lithium levels and suicide mortality in the population, some authors have suggested careful consideration of fortifying tap water with microdose lithium (Ng et al., 2019; Szklarska and Rzymski, 2019).

Hungary had a notoriously high suicide rate in the last century, with regional differences that have been fairly stable over time (Balint et al., 2014). Hungary therefore seems to be ideal for studying the supposed association between tap water lithium levels and suicide rate. We selected confounding variables (i.e. income, alcohol consumption and religiosity) to include in our calculations that were previously reported to affect suicide risk (Balint et al., 2014; Bálint et al., 2016; Conner and Bagge, 2019; Näher et al., 2019; Pompili et al., 2010; Qin et al., 2003; Saiz et al., 2021; Sareen et al., 2011; Vichi et al., 2020). As far as we know, no such study has previously been conducted using Hungarian data.

## 2. Methods

### 2.1. Data

Suicide cases, tabulated by age and gender, for the period investigated (2005–2015) came from the demographic database ("Demo") of the Hungarian Central Statistical Office (HCSO). In the database an individual whose International Classification of Diseases-10 (ICD-10) code in the paragraph "cause of death" was one of the following was considered as a suicide completer: X60 to X84. Suicide victims under 15 years of age were excluded due to the very low number of cases in that age group. In 2011, the number of Hungarian subjects aged 15 and above was 8 495 001. Suicide victims were grouped according to their place of residence. During the period investigated 25 571 completed suicide cases were documented among those above 15 years of age in Hungary (male = 19 595; female = 5 976). Those few cases ($n$ = 233 [male = 204; female = 29] during the whole study period) where the place of residence and/or age were unknown (e.g. in the case of homeless people) were excluded. In calculations carried out separately by gender, for the *dependent variable* we used the age-standardized (with the indirect method using 5-year age-groups) mortality ratios for suicide (***sSMR***) for every Hungarian district ($n = 197$; the number of inhabitants aged 15 and above ranged between 7 818 and 213 893 [mean = 43 564] in 2011). In calculations carried out for the total population (i.e. males and females together), we used the age- and gender-standardized SMRs for every Hungarian district as the dependent variable. In regression models, the natural logarithm of ***sSMR*** was used in order to achieve constant variance and proper functional form.

Our main explanatory variable was the lithium level in the drinking water aggregated to the district level. Every Hungarian public drinking water supply system using its own water source ($n = 1\ 325$) was sampled and lithium levels were measured (the sampling procedure and measurement are discussed in detail at the end of this paragraph). Subsequently, we determined the tap water lithium levels of all Hungarian settlements ($n = 3\ 176$), i.e. lithium data from the water supplies were assigned to the supplied settlements. Where more than one water supply system provided tap water to a given settlement (67 out of 3 176), average lithium concentrations were calculated, with the average values taken as representing the lithium levels of the given settlements. The settlement level data cover all households connected to the public water supply, and, in this way, approximately 95% of Hungarian households (HCSO, https://www.ksh.hu/docs/hun/xstadat/xstadat_eves/i_zrk005a.html). To obtain district-level data, lithium levels of settlements were aggregated, weighted by the population of the settlements. In the final step, these aggregated lithium levels were natural log-transformed. All public drinking water supply systems using their own water source ($n = 1\ 325$) were sampled between January 2016 and July 2018. Samples were collected in plastic (PP) containers. Before sample analysis, the pH of samples was reduced below 2 by high-purity nitric acid. Lithium levels were analyzed by inductively coupled plasma-mass spectrometry (ICP-MS) in accordance with the MSZ EN ISO 17,294 standard. The limit of quantification (LOQ) was 1 μg/l, the limit of detection (LOD) was 0,1 μg/l. Since values under the LOQ are not reliable, in the calculations below, $<$LOQ values were replaced by LOQ/$\sqrt{2}$. In order to evaluate the temporal variability of lithium in the water sources, two subsets of sampling sites were resampled between April 2018 and August 2020. The areas were selected based on the lithium concentrations in drinking water: in one group, the concentrations were typically low ($n = 43$), while in the other group they were typically high ($n = 41$). Samples were collected and analyzed as described above.

We used the HCSO database “Demo” for calculating age- and/or gender-standardized mortality rates due to alcoholic liver disease (ICD-10 codes: K70.0; K70.1; K70.2; K70.3; K70.4 and K70.9) for the period investigated (2005–2015). These were calculated for each population investigated (i.e. male, female, total) and for each district (the abbreviation of this variable is ***ALC***). Age standardization was carried out using the indirect method with 5-year age-groups.

The variable *religiosity* (hereinafter abbreviated as ***REL***) for a given district was assessed according to the proportion of persons who declared themselves as “belonging to any church/denomination” in the 2011 Census. In contrast to our variables ***sSMR*** and ***ALC***, we were unable to specify the gender-specific measure of religiosity. The source of this variable was the database “TEIR” (https://www.teir.hu/).

*Income* was calculated based on the amount of personal income tax paid per capita in a given district between 2005 and 2015 and indexed to the 2015 value (the abbreviation of this variable is ***INC***). In contrast to our variables ***sSMR*** and ***ALC***, we were unable to specify the gender-specific measure of income. The source of this variable was the database TEIR (https://www.teir.hu/). In calculations, the natural log-transformed form of ***INC*** was used.

### 2.2. Statistical methods

First we investigated the associations between our variables through the Ordinary Least Square (OLS) regression. Due to the strong autocorrelation, the behavior of the error terms in the OLS regression violates the assumption of independence of the error terms. Accordingly, then we conducted two different spatial approaches, namely the Maximum Likelihood Spatial Lag (ML-Lag) and the Spatial Two-Stage Least Squares (STSLS) models. Using OLS residuals, the decision between whether to apply the Spatial Lag or the Spatial Error model was based on the results of the Lagrange Multiplier ($LM_{err}$ and $LM_{lag}$) and the Robust Lagrange Multiplier Tests ($RLM_{err}$ and $RML_{lag}$). Higher values of the results of these tests (along with their lower $p$ values) indicate which model is more appropriate to use. According to the test diagnostics, we deemed the use of the Spatial Lag model more appropriate. Residuals of the OLS and the ML-Lag models were assessed for heteroscedasticity using the Breusch-Pagan test, while the normal distribution of the residuals was assessed using the Jarque–Bera test. Due to the endogeneity of the spatially lagged dependent variable and the strong heteroscedasticity we decided also to use the STSLS approach. In the first step of the Two-Stage Least Squares method, each of the endogenous variables is regressed with all exploratory variables (exogenous variables) and instruments. Then the predicted values of this regression are used as independent predictors, replacing the endogenous variables. The STSLS estimator is an extension of the standard Two-Stage Least Squares estimator that includes specific instruments for the spatially lagged dependent variable (as the endogenous variable) (Anselin, 1988, 2017; Anselin and Lozano-Gracia, 2008; Anselin and Rey, 2014; Balint, 2010). To compare the overall model fit of the OLS and the ML-Lag regression models, we used the Akaike Information Criterion (AIC), in which lower values indicate better fit of the model. LM and Moran’s I tests were used to help identify the existence of spatial dependence in the regression models. The presence of multicollinearity between our explanatory variables was examined by calculating the “multicollinearity condition number”. To handle the high level of multicollinearity identified within our initial set of explanatory variables, we had to omit some of them (i.e. marital status and population density) from the final calculations. The aforementioned statistical calculations were conducted using the ‘R’ language, including its ‘spdep’ and ‘spatialreg’ packages (Bivand and Piras, 2015; Bivand et al., 2013; https://www.r-project.org/).

The Shapiro-Wilk (S-W) test was used to verify the normal distribution of lithium levels from the first and second samplings of those water sources ($n = 84$) where we had the opportunity for a repeat sampling. The results show that the distributions were not normal for samples from either sampling. Accordingly, the temporal stability of lithium levels was assessed by Spearman correlation. Correlation calculations and S-W test were carried out using the IBM-SPSS (version 24) software.

## 3. Results

### 3.1. Descriptive statistics for lithium levels and standardized mortality ratios for suicide (sSMR)

The lithium levels in the drinking water at the level of settlements ($n = 3\ 176$) ranged from 0.71 (i.e. LOQ/$\sqrt{2}$) to 302.7 μg/L (mean = 14.3 μg/L; SD = 21.7 μg/L). Lithium levels aggregated to the level of districts ranged from 0.71 to 89.35 μg/L (mean = 11.214; SD = 11.949) (Fig. 1; Table 1).

Gender- and age-standardized ***SMRs*** for suicide in the *total* population ranged from 0.492 to 2.138 (mean = 1.082; SD = 0.353) (Table 1; Fig. 2).

Age-standardized ***SMRs*** for suicide in the *male* population ranged from 0.467 to 2.382 (mean = 1.093; SD = 0.371) (Table 1; Fig. 3). Corresponding figures for females ranged from 0.235 to 2.505 (mean = 0.996; SD = 0.397) (Table 1). Descriptive statistics of all variables involved in the study can be found in Table 1.

### 3.2. Results from the regression models

In the *male* subpopulation, lithium levels were associated negatively with ***sSMR*** in a significant (i.e. $p < 0.05$) and a trend-like fashion (i.e. $p < 0.1$) in the OLS and STSLS models, respectively (Table 2).

Among *females*, neither regression model revealed significant associations between lithium levels and ***sSMR*** (Table 3). It is possible that the lack of significant associations in women is due to the relatively low number of suicides among them (compared to males).

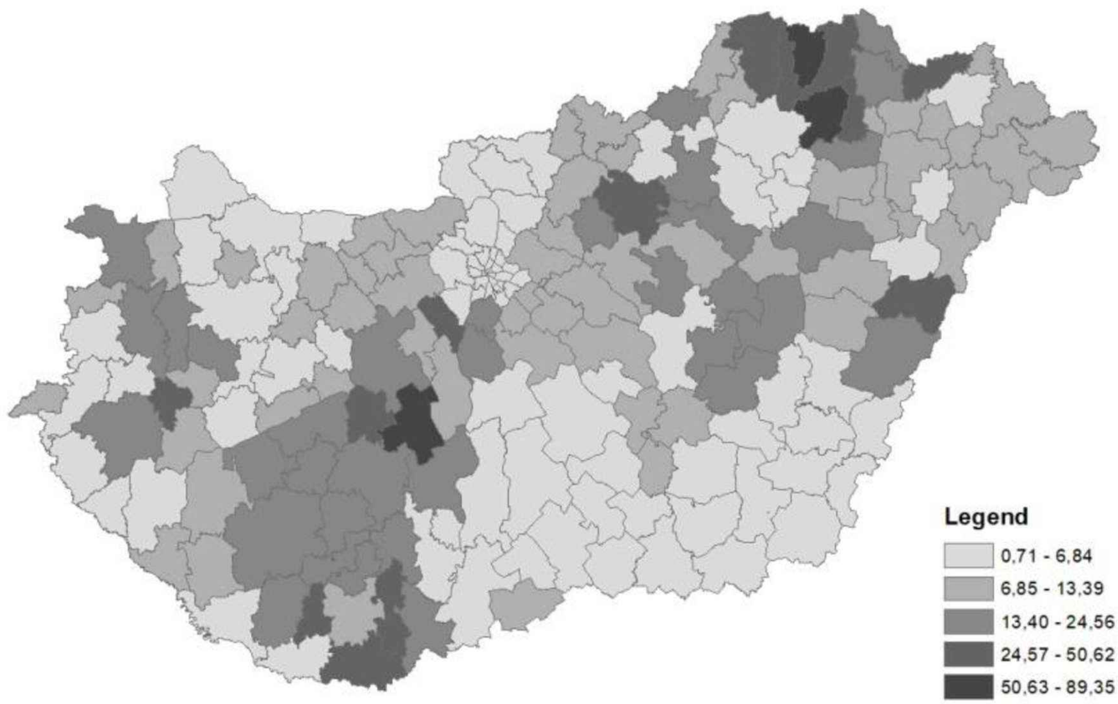


**Fig. 1.** Lithium levels aggregated (weighted by the population of the settlements) to the level of districts (levels expressed in μg/L).

**Table 1**
Descriptive statistics of variables at the level of districts.

| | n | mean | S.D. | median | min. | max. | skew | kurtosis | Moran's I |
|---|---|---|---|---|---|---|---|---|---|
| ***sSMR; male*** (not log-transformed) | 197 | 1.093 | 0.371 | 1.03 | 0.467 | 2.382 | 0.582 | −0.194 | 0.690*** |
| ***sSMR; female*** (not log-transformed) | 197 | 0.996 | 0.397 | 0.938 | 0.235 | 2.505 | 0.828 | 0.879 | 0.488*** |
| ***sSMR; total*** (not log-transformed) | 197 | 1.082 | 0.353 | 1.018 | 0.492 | 2.138 | 0.707 | −0.227 | 0.670*** |
| ***Lithium*** (not log-transformed) | 197 | 11.214 | 11.949 | 7.75 | 0.707 | 89.347 | 3.394 | 15.676 | 0.403*** |
| ***INC*** (not log-transformed) | 197 | 690,213.3 | 212,748.4 | 639,430.8 | 347,664.9 | 1,443,148 | 0.985 | 0.785 | 0.732*** |
| ***REL*** | 197 | 58.578 | 12.653 | 59.455 | 30.467 | 84.227 | −0.076 | −1.099 | 0.689*** |
| ***ALC; male*** | 197 | 1.065 | 0.318 | 1.038 | 0.311 | 2.199 | 0.386 | 0.048 | 0.475*** |
| ***ALC; female*** | 197 | 1.003 | 0.308 | 0.966 | 0.271 | 1.917 | 0.256 | −0.272 | 0.330*** |
| ***ALC; total*** | 197 | 1.061 | 0.29 | 1.036 | 0.339 | 1.935 | 0.31 | −0.221 | 0.451*** |

**S.D.**: standard deviation

With regard to the *total* population, a pattern similar to that of the male subpopulation was found (i.e. OLS and STSLS models showed significant negative associations between lithium levels and ***sSMR***) (Table 4).

As was expected, according to the results of OLS, ML-Lag and STSLS models, the variables ***INC*** and ***REL*** were significantly negatively associated with ***sSMR*** in each population investigated (i.e. total, female, male) (**Tables 2, 3 and 4**). Somewhat surprisingly, **ALC** was not significantly associated with ***sSMR*** in either population investigated (Tables 2, 3 and 4).

### 3.3. *Temporal stability of lithium in drinking water*

In the case of some water sources ($n = 84$), we had the opportunity for resampling (the mean time between taking the first and second samples was 770 days), allowing us to assess the time-dependent stability of lithium levels by calculating the correlation between the lithium levels from the first and second samples. Although literature data on the temporal variation of lithium in drinking water and source water is limited, it is generally considered stable due to the small size and strong hydration of lithium ion in aqueous solutions (Knudsen et al., 2017). For instance, Ohgami et al. reported a very high correlation between lithium levels in samples from the same places with a 1-year interval between the samplings (Ohgami et al., 2009). Our results (Spearman's rho=0.921; $p<0.001$) support the temporal stability of lithium levels.

## 4. Discussion

Besides clozapine (which is FDA-approved for suicide prevention in subjects with schizophrenia), lithium is the only medication with strongly proven suicide-preventive features (Barroilhet and Ghaemi, 2020; Gitlin, 2020; Hidvégi et al., 2016; McIntyre et al., 2020; Taipale et al., 2021). As we have already discussed in the Introduction, multiple lines of evidence supported the conjecture that trace amounts of lithium in drinking water may be bioactive *in genere* and have suicide-preventive effects *in specie*.

The present research investigated statistically the association between natural lithium levels in drinking water and suicide mortality at the level of districts ($n = 197$) in Hungary. Results of the OLS and STSLS models suggest a significant negative association between tap water lithium levels and ***sSMR*** in the total Hungarian population. For males, results indicated that lithium has a significant (i.e. $p < 0.05$) and a trend-level (i.e. $p < 0.1$) suicide-protective effect in the OLS and the STSLS models, respectively. By contrast, neither regression model indicated that there is a similar inverse association between lithium levels and ***sSMR*** among females. To sum up, in line with the majority of previous

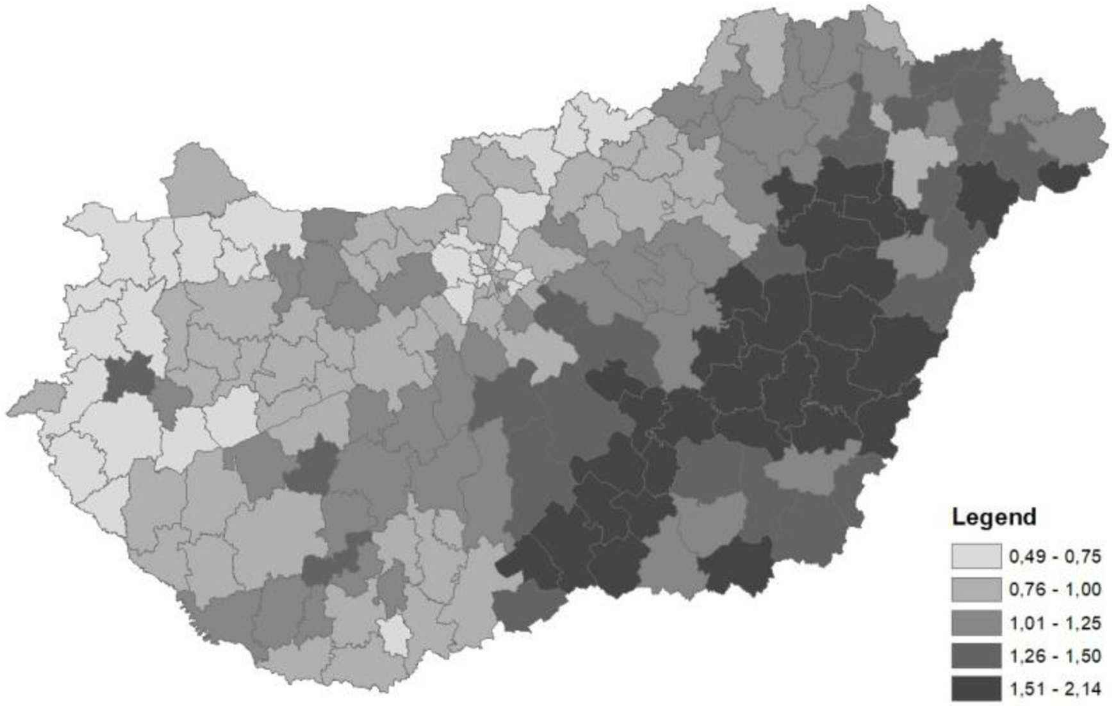


**Fig. 2.** Gender- and age-standardized ***SMRs*** for suicide; total population.

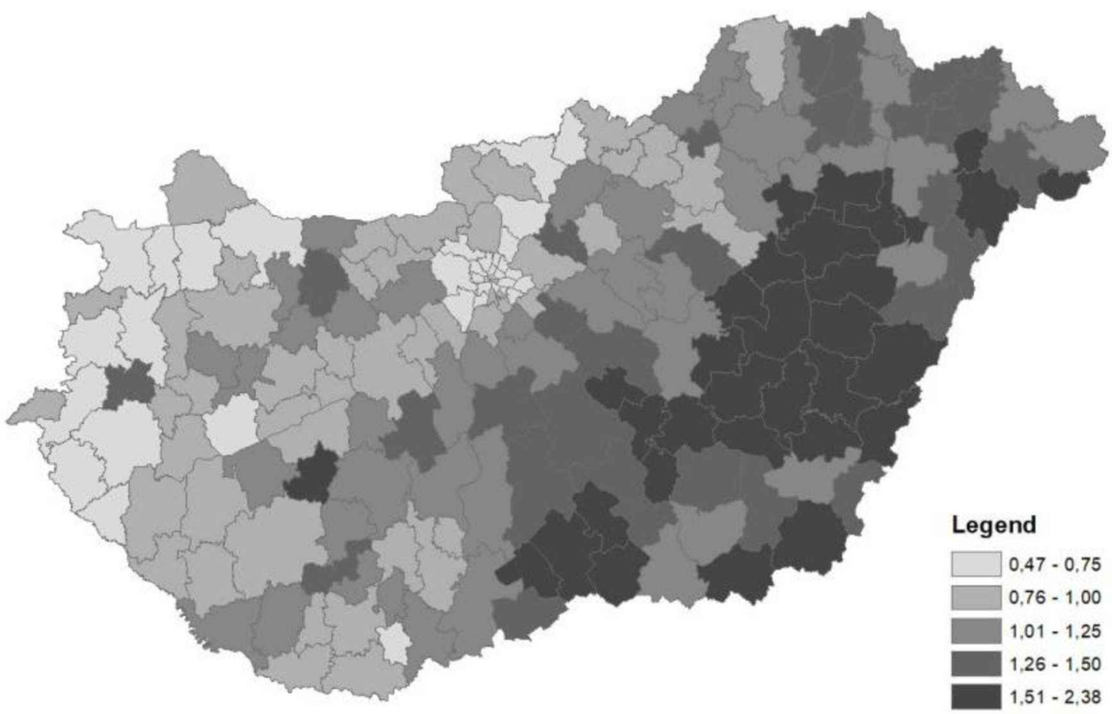


**Fig. 3.** Age-standardized ***SMRs*** for suicide; males.

results (Barjasteh-Askari et al., 2020; Del Matto et al., 2020), our findings suggest that there may be an inverse association between tap water lithium levels and ***sSMR*** among males, but not among females. This gender difference may be due to the fact that 1) males frequently use more violent methods to commit suicide than females; 2) lithium may decrease suicidality by reducing impulsivity and aggression (Barjasteh-Askari et al., 2020; Del Matto et al., 2020). Although the results are somewhat ambiguous, a similar phenomenon may be seen among subjects treated with lithium. For instance, Kessing et al. found that the great male preponderance in suicide found in the general population was eliminated among subjects purchasing lithium (Kessing et al., 2005). With regard to our further explanatory variables, we found that religiosity and income were negatively associated with ***sSMR*** in each population investigated (i.e. male, female and total). As higher levels of religiosity and income were reported as important negative predictors for suicidal behavior, our auxiliary findings are in line with the previous

**Table 2**
Results from the regression models for the male population.

| Variables | OLS Coefficients | Std. error | ML-Lag Coefficients | Std. error | STSLS Coefficients | Std. error |
|---|---|---|---|---|---|---|
| Intercept | 15.627*** | 0.903 | 8.138*** | 1.013 | 9.032*** | 1.156 |
| Lithium | −0.040* | 0.018 | −0.023 | 0.014 | −0.025† | 0.013 |
| ***INC*** | −1.098*** | 0.063 | −0.575*** | 0.071 | −0.633*** | 0.081 |
| ***REL*** | −0.010*** | 0.002 | −0.005*** | 0.001 | −0.006*** | 0.001 |
| ***ALC*** | 0.012 | 0.057 | 0.066 | 0.044 | 0.011 | 0.052 |
| $\rho$ | | | 0.575*** | | 0.522*** | 0.074 |
| **Diagnostics** | | | | | | |
| Condition Number | 12.976 | | | | | |
| Breusch-Pagan test | 10.994* | | 24.15*** | | | |
| Jarque-Bera test | 25.36*** | | 51.888*** | | | |
| Moran's I | 0.335 | | 0.008 | | | |
| Adj. $R^2$ / pseudo $R^2$ | 0.610 | | 0.761 | | | |
| AIC | −41.146 | | −116.76 | | | |
| **LM Tests** | | | | | | |
| $LM_{err}$ | 57.601*** | | | | | |
| $LM_{lag}$ | 78.572*** | | | | | |
| $RLM_{err}$ | 3.568 | | | | | |
| $RLM_{lag}$ | 24.539*** | | | | | |

***$p < 0.001$, **$p < 0.01$, *$p < 0.05$; †$p < 0.1$; **(R)LM$_{(err/lag)}$**: (Robust) Lagrange multiplier test (error or lag); **AIC**: Akaike information criterion; **ρ**: Spatial autoregressive parameter; **OLS**: Ordinary Least Square regression; **ML-Lag**: Maximum Likelihood Spatial Lag regression; **STSLS**: Spatial Two-Stage Least Squares regression.

**Table 3**
Results from the regression models for the female population.

| Variables | OLS Coefficients | Std. error | ML-Lag Coefficients | Std. error | STSLS Coefficients | Std. error |
|---|---|---|---|---|---|---|
| Intercept | 10.639*** | 1.442 | 6.399*** | 1.426 | 5.616** | 1.827 |
| Lithium | −0.046 | 0.028 | −0.019 | 0.025 | −0.019 | 0.029 |
| ***INC*** | −0.694*** | 0.101 | −0.418*** | 0.099 | −0.367** | 0.123 |
| ***REL*** | −0.019*** | 0.002 | −0.012*** | 0.002 | −0.010*** | 0.003 |
| ***ALC*** | −0.069 | 0.081 | −0.021 | 0.072 | −0.008 | 0.087 |
| $\rho$ | | | 0.484*** | | 0.610*** | 0.144 |
| **Diagnostics** | | | | | | |
| Condition Number | 13.76 | | | | | |
| Breusch-Pagan test | 20.173*** | | 26.307 | | | |
| Jarque-Bera test | 3.866 | | 15.071 | | | |
| Moran's I | 0.251 | | −0.042 | | | |
| Adj. $R^2$ / pseudo $R^2$ | 0.3065 | | 0.4292 | | | |
| AIC | 144.91 | | 112.58 | | | |
| **LM tests** | | | | | | |
| $LM_{err}$ | 32.343*** | | | | | |
| $LM_{lag}$ | 42.938*** | | | | | |
| $RLM_{err}$ | 0.197 | | | | | |
| $RLM_{lag}$ | 10.791** | | | | | |

***$p < 0.001$, **$p < 0.01$, *$p < 0.05$; †$p < 0.1$; **(R)LM$_{(err/lag)}$**: (Robust) Lagrange multiplier test (error or lag); **AIC**: Akaike information criterion; **ρ**: Spatial autoregressive parameter; **OLS**: Ordinary Least Square regression; **ML-Lag**: Maximum Likelihood Spatial Lag regression; **STSLS**: Spatial Two-Stage Least Squares regression.

findings (Näher et al., 2019; Qin et al., 2003; Saiz et al., 2021; Sareen et al., 2011). Although several previous studies have demonstrated that alcohol consumption is a risk factor for suicide, in the current study no significant associations were found between our proxy variable for alcohol consumption (i.e. the mortality due to alcoholic liver diseases) and suicide mortality (Conner and Bagge, 2019; Pompili et al., 2010). A strength of our study is that lithium concentrations data at the district level were based on samples from a large number of public water supply systems ($n = 1$ 325). Ecological studies with negative findings come mainly from countries where the range of tap water lithium levels and/or suicide rates were found to be low (Del Matto et al., 2020; Oliveira et al., 2019). In view of the latter point, we consider that Hungary with its notoriously high suicide mortality is an ideal country for investigating the supposed association between tap water lithium levels and suicide mortality.

Some limitations should be taken into account when interpreting our findings. First of all, like the vast majority of relevant previous studies, we carried out our calculations using aggregate (i.e. non-individual) data, which may result in the methodological drawback named "ecological fallacy" (Barjasteh-Askari et al., 2020; Robinson, 1950). This means that our results and conclusions are not necessarily true on the level of individuals (Balint et al., 2014). Another major limitation of the study is that several important psychiatric variables were unavailable at the district level (e.g. prevalence rates for mood disorders, antidepressant and mood stabilizer [including lithium] utilization). Nevertheless, the relatively good model fits indicate that the extent of the bias due to omitted variables cannot be considerable. In addition, since we had no data on previous place(s) of residence of suicide victims (if they had any), we were unable to assess their lifetime exposure levels to lithium from drinking water. To our best knowledge, with one exception (Knudsen et al., 2017), this was a shortcoming of all other similar studies conducted so far (Barjasteh-Askari et al., 2020). Another limitation of the study is that we were unable to assess the level of bottled mineral water consumption and dietary patterns at the levels of districts, which is presumed to influence the lithium exposure of individuals (Enderle et al., 2020). Finally, in the case of 296 out of the 3 176 settlements included, technological changes were made in the water supply systems before our water sampling period (2016–2018). We are unaware of the

**Table 4**
Results from the regression models for the total population.

| Variables | OLS Coefficients | Std. error | ML-Lag Coefficients | Std. error | STSLS Coefficients | Std. error |
|---|---|---|---|---|---|---|
| Intercept | 14.658*** | 0.853 | 7.591*** | 0.958 | 9.074*** | 1.103 |
| Lithium | −0.040* | 0.017 | −0.020 | 0.013 | −0.027* | 0.013 |
| ***INC*** | −1.017*** | 0.059 | −0.531*** | 0.067 | −0.629*** | 0.076 |
| ***REL*** | −0.011*** | 0.001 | −0.006*** | 0.001 | −0.007*** | 0.001 |
| ***ALC*** | −0.060 | 0.057 | 0.031 | 0.044 | −0.029 | 0.055 |
| $\rho$ | | | 0.590*** | | 0.483*** | 0.079 |
| **Diagnostics** | | | | | | |
| Condition Number | 12.5321 | | | | | |
| Breusch-Pagan test | 20.262*** | | 19.871*** | | | |
| Jarque-Bera test | 2.8908 | | 23.636*** | | | |
| Moran's I | 0.3736*** | | 0.018 | | | |
| Adj. $R^2$ / pseudo $R^2$ | 0.5975 | | 0.73969 | | | |
| AIC | −62.6048 | | −142.39 | | | |
| **LM tests** | | | | | | |
| $LM_{err}$ | 71.507*** | | | | | |
| $LM_{lag}$ | 86.051*** | | | | | |
| $RLM_{err}$ | 6.2655* | | | | | |
| $RLM_{lag}$ | 20.809*** | | | | | |

***$p < 0.001$, **$p < 0.01$, *$p < 0.05$; †$p < 0.1$; **(R)LM$_{(err/lag)}$**: (Robust) Lagrange multiplier test (error or lag); **AIC**: Akaike information criterion; **ρ**: Spatial autoregressive parameter; **OLS**: Ordinary Least Square regression; **ML-Lag**: Maximum Likelihood Spatial Lag regression; **STSLS**: Spatial Two-Stage Least Squares regression.

impact of those changes on the lithium levels. Accordingly, it is conceivable that in the period when suicide cases were monitored (2005–15) tap water lithium levels in a minority of settlements differed from those measured later (i.e. in the sampling period between 2016 and 2018).

In conclusion, our results from a country with traditionally high rates of suicide indicate that trace amounts of lithium in tap water may have suicide-protective effects among males, but not among females. These results show a close match with the findings of the majority of previous studies.

## Authors' contributions

BI, AH, PD, LB, MV, TP, TM and ZR conceived and designed the study idea. BI and LB gathered the raw data. Statistical calculations were carried out by LB. PD, AH and BI managed literature searches and wrote the first draft of the manuscript. LB designed the figures. All authors critically reviewed the first version of the manuscript and contributed to the final version of the manuscript.

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## Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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