The British Journal of Psychiatry

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The British Journal of Psychiatry 2011 198: 346-350
Access the most recent version at doi:10.1192/bjp.bp.110.091041

BJPsych
The British Journal of Psychiatry (2011)
198, 346–350. doi: 10.1192/bjp.bp.110.091041

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Background
There is some evidence that natural levels of lithium in drinking water may have a protective effect on suicide mortality.

Aims
To evaluate the association between local lithium levels in drinking water and suicide mortality at district level in Austria.

Method
A nationwide sample of 6460 lithium measurements was examined for association with suicide rates per 100 000 population and suicide standardised mortality ratios across all 99 Austrian districts. Multivariate regression models were adjusted for well-known socioeconomic factors known to influence suicide mortality in Austria (population density, per capita income, proportion of Roman Catholics, as well as the availability of mental health service providers). Sensitivity analyses and weighted least squares regression were used to challenge the robustness of the results.

Results
The overall suicide rate ($R^2=0.15$, $\beta=-0.39$, $t=-4.14$, $P=0.000073$) as well as the suicide mortality ratio ($R^2=0.17$, $\beta=-0.41$, $t=-4.38$, $P=0.000030$) were inversely associated with lithium levels in drinking water and remained significant after sensitivity analyses and adjustment for socioeconomic factors.

Conclusions
In replicating and extending previous results, this study provides strong evidence that geographic regions with higher natural lithium concentrations in drinking water are associated with lower suicide mortality rates.

Declaration of interest
None.

Natural lithium traces in water were considered by John Cade in 1949 to have the potential to influence mental health.[1] Meanwhile, the mood-stabilising effects of lithium are widely recognised by the psychiatric community[2] and its suicide preventive properties are well documented.[3] Although the effects of therapeutic doses of lithium are well established, little is known about the health effects of natural lithium intake.

As a natural trace element, lithium is mobilised by rain from rock and soil and dissolves in ground and drinking water. In some geographic regions, its concentrations may reach up to 5.2 mg/l, reflecting a natural daily intake of lithium of up to 10 mg/day.[4,5] Although such daily doses of lithium are considerably lower than those used therapeutically, it is unknown to what extent intake of natural lithium may influence mental health or suicide mortality. Only one randomised placebo-controlled study showed favourable effects of low-dose lithium supplementation (0.4 mg daily) on mood, in a small sample of former drug users.[6] However, evidence from ecological studies indicates that lithium levels in drinking water may be associated with regional suicide mortality. The first study was carried out in Texas in 1990 and demonstrated that counties with higher lithium levels in municipal water supplies had lower suicide and crime rates.[7] A more recent report from Japan showed an inverse relationship between lithium levels in tap water and suicide mortality in Oita prefecture.[8] However, this report has been criticised for being based on unreliable lithium measures,[9] and for omitting socioeconomic confounders such as poverty and economic issues.[10] In order to replicate the report of Ohgami *et al*[8] on the basis of data originating from a different country, and to address the criticisms mentioned above, we extended the design of the study by Ohgami and colleagues and used a large data source of lithium levels in drinking water. To challenge the hypothesis that lithium levels in drinking water are inversely associated with suicide mortality, we adjusted for regional socioeconomic conditions and the availability of mental health service providers. These factors were recently shown to influence suicide mortality in Austria.[11]

Method

Statistics Austria provided the official Austrian mortality database for suicides in 17 age groups and both genders for 99 Austrian districts and for each year in the time period 2005–2009. Comprehensive data on population density, average income per capita and the proportion of Roman Catholics were obtained from the official Austrian population census 2001 (www.statistik.at). The unemployment rates were obtained from the Austrian Public Employment Service (AMS) (M. Eichinger, personal communication, 2009) and were averaged for the available years 2005–2008. All consecutive years were strongly correlated ($r>0.9$). The density of general practitioners (GPs) and psychiatrists per 10 000 population for each district were available for the year 2007 from the Austrian Medical Chamber (A. Sinabell, personal communication, 2009). The Austrian Institute of Health (ÖBIG)[12] provided figures on the density of psychotherapists per 100 000 for the year 2005. Austria had an average population of 8 297 964 (s.d. = 65 050) during the examined time period 2005–2009. The average population per district was 83 818 (s.d. = 165 643), with a range of 1714 to 1 667 878 inhabitants (capital city Vienna). Excluding Vienna (by far the largest region) produced an average population per district of 67 654 (s.d. = 39 852).

To account for the distributions of gender and age in each district, we calculated standardised mortality ratios (SMRs) for suicide for each district using the indirect method, by taking the gender and age composition of the general population as a standard. Although using SMR is formally more appropriate than computing with suicide rates per 100 000 in epidemiological and ecological studies,[13] we applied both methods for each district to allow discussion of estimated effects as recently suggested.[9]

Lithium levels were obtained from AQA GmbH, an Austrian company engaged in the collection and the analysis of drinking water samples and applied scientific research. The samples were analysed by inductively coupled plasma optical emission spectrometry, a method for the determination of dissolved inorganic, organic and other compounds in water samples.[14] The sample data were collected between 2005 and autumn 2010. In total, 6460 water samples from drinking water supplies from all 99 districts were analysed for lithium (see online Figs DS1 and DS2). The average was 65.3 samples per district (range 1–312). The lowest measurable threshold lithium level by inductively coupled plasma optical emission spectrometry was 0.0033 mg/l. Subthreshold values were found in seven districts. For the statistical calculations, lithium levels were averaged per district. The mean lithium level in Austrian drinking water was 0.0113 mg/l (s.d. = 0.027). The highest single lithium level was found in Graz-vicinity (1.3 mg/l), and the district with the highest mean level was Mistelbach (0.0823 mg/l).

To allow for comparison with the results of the Japanese study,[8] we used similar statistical methods; although more elaborated methods for the analysis of geographical data have already been applied.[11] Because of the skewness of the distribution of lithium levels (skewness 4.606, kurtosis 27.134), the population density, the density of psychiatrists, psychotherapists and GPs, the variables were log-transformed to fit non-parametric tests. Prior to the log-transformation, we also applied a conservative sensitivity analysis of the crude regression model of overall suicide rates as well as SMRs for suicide and lithium levels by inspection of scatter plots and boxplots for the identification of outliers. In total, seven possible outlier districts were identified: Rust-city, Eisenstadt-vicinity, Oberwart, Bruck an der Leitha, Hollabrunn, Korneuburg and Mistelbach. However, exclusion of these outliers did not alter the direction of the association between suicide rates or SMR for suicide and lithium levels nor exceeded the significance level set at alpha 0.05 for all analyses. The same was true when districts with less than five water samples were excluded, or Vienna, the largest city, was excluded (these complementary analyses are not reported in the results). Therefore, all further regression models were based on log-transformed data of all 99 districts.

Weighted least squared (WLS) regression analyses adjusted for the size of the population per district were employed to test for the robustness of univariate and multivariate statistics. Multivariate regression models incorporated those covariates that were significantly correlated with SMR for suicide (Table 1) in correlation tests. The residuals in the regression models were inspected in plots and tested with the Kolmogorov–Smirnoff test for normality. Possible auto-regression of data was analysed using the Durbin–Watson tests. Multivariate models were tested for multicollinearity by calculating tolerance values and the condition index. Data analysis was performed on SPSS 17.0 for Windows.

Results

Suicide mortality was significantly correlated with mean lithium levels per district, population density, per capita income, the proportion of Roman Catholics, as well as with the density of psychiatrists, psychotherapists and GPs. Unemployment did not correlate with suicide mortality (Table 1).

Univariate regression

The univariate regression parameters for the untransformed lithium levels as the independent variable were similar for the overall suicide rate per 100 000 ($R^2 = 0.15$, $\beta = -0.39$, $t = -4.14$, $P = 0.000073$), suicide rates for males ($R^2 = 0.12$, $\beta = -0.35$, $t = -3.64$, $P = 0.00043$) and females ($R^2 = 0.08$; $\beta = -0.28$, $t = -2.82$, $P = 0.0058$) (online Fig. DS3). The results were comparable when SMRs were used instead of suicide rates: overall ($R^2 = 0.17$, $\beta = -0.41$, $t = -4.38$, $P = 0.000030$), male ($R^2 = 0.13$; $\beta = -0.36$, $t = -3.84$, $P = 0.00022$) and female SMR ($R^2 = 0.08$, $\beta = -0.29$, $t = -2.96$, $P = 0.0038$) (Fig. 1).

Log-transformed regressions

All further analyses were based on log-transformed data (online Fig. DS4 and Fig. 2). The univariate regression estimates of lithium as a predictor were comparable for overall ($R^2 = 0.14$, $\beta = -0.38$, $t = -4.01$, $P = 0.00012$), male ($R^2 = 0.11$, $\beta = -0.33$, $t = -3.39$, $P = 0.00098$) and female SMRs ($R^2 = 0.09$; $\beta = -0.29$, $t = -3.02$, $P = 0.0032$). Weighting (WLS) for the number of inhabitants per district revealed significant associations for the overall SMR ($R^2 = 0.05$, $\beta = -0.22$, $P = 0.029$), females ($R^2 = 0.04$, $\beta = -0.21$, $P = 0.037$) and a trend for males ($R^2 = 0.03$, $\beta = -0.18$, $P = 0.083$).

Multivariate regression

Lithium levels remained as a significant predictor in the unweighted multivariate model (Table 2). Lithium also remained

Table 1 Correlation between district characteristics and standardised mortality ratios (SMR) for suicide (2005–2009)[a]

	Suicide SMR					
	Overall		Male		Female	
District characteristics	*r*	*P*	*r*	*P*	*r*	*P*
Lithium level, mean (mg/l)	**−0.406**	0.000030	**−0.364**	0.00021	**−0.288**	0.0038
Log lithium level	**−0.377**	0.00012	**−0.326**	0.0098	**−0.294**	0.0032
Population density (per km)	**−0.213**	0.034	**−0.223**	0.026	−0.018	0.858
Log population density	**−0.291**	0.0034	**−0.295**	0.0030	−0.058	0.571
Per capita income (in 1000 Euro)	**−0.306**	0.0021	**−0.292**	0.0034	−0.143	0.158
Proportion of Roman Catholics, %	**0.398**	0.000045	**0.398**	0.000044	0.140	0.166
Unemployment rate, %	−0.143	0.160	−0.089	0.382	−0.183	0.071
Psychiatrist density (per 10 000)	**−0.284**	0.0043	**−0.313**	0.0016	−0.019	0.850
Log psychiatrist density	**0.452**	0.0000048	**0.478**	0.0000011	−0.066	0.527
Psychotherapist density (per 10 000)	**−0.231**	0.021	**−0.246**	0.014	−0.011	0.916
Log psychotherapist density	**−0.470**	0.0000012	**−0.493**	0.00000028	−0.063	0.542
General practitioner density (per 10 000)	**−0.244**	0.015	**−0.240**	0.017	−0.068	0.503
Log general practitioner density	**−0.223**	0.027	**−0.215**	0.033	−0.067	0.512

a. Results in bold are significant.

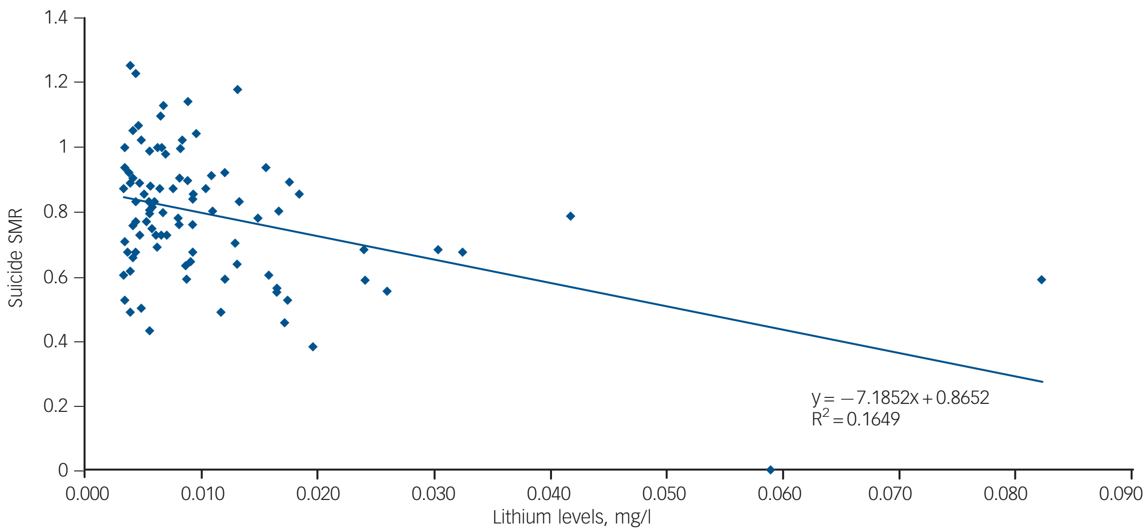

Fig. 1 Crude lithium levels and standardised mortality ratios (SMRs) for suicide (2005–2009).

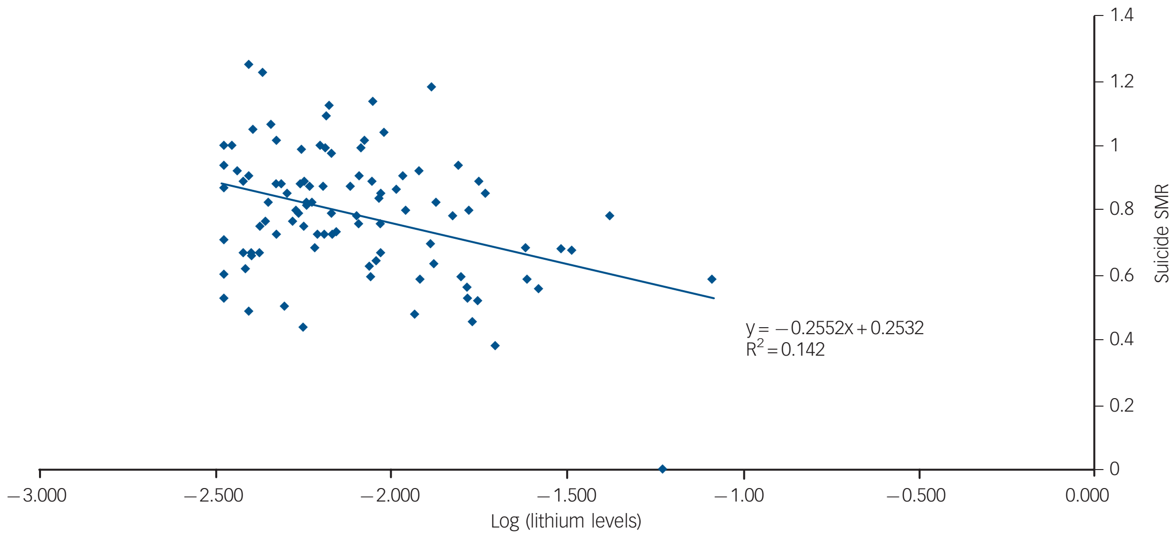

Fig. 2 Log-transformed lithium levels and standardised mortality ratios (SMRs) for suicide (2005–2009).

Table 2 Multivariate regression estimates on overall standardised mortality ratios (SMRs) for suicide (2005-2009)[a]

	$\hat{a}$	*T*	*P*	R^2	R^2_{adj}	D–W[b]
Overall suicide SMR				0.372	0.321	2.236
Constant		0.092	0.927			
Log lithium level	−0.309	−3.254	**0.0016**			
Log population density	0.120	0.787	0.434			
Per capita income	−0.112	−0.955	0.342			
Proportion of Roman Catholics	0.101	0.858	0.393			
Log psychiatrist density	−0.260	−1.774	0.080			
Log psychotherapist density	−0.364	−2.199	**0.031**			
Log general practitioner density	0.184	1.663	0.100			
Overall suicide SMR (WLS)[c]				0.377	0.326	2.250
Constant		0.118	0.906			
Log lithium level	−0.243	−2.328	**0.022**			
Log population density	0.213	1.167	0.246			
Per capita income	−0.226	−1.570	0.120			
Proportion of Roman Catholics	0.112	0.713	0.478			
Log psychiatrist density	−0.335	−2.156	**0.034**			
Log psychotherapist density	−0.326	−1.656	0.101			
Log general practitioner density	0.263	2.308	**0.023**			

a. Results in bold are significant.
b. Durbin–Watson test for autocorrelation.
c. Weighted least squares (WLS) regression adjusted for population per district.

significant in the models for females ($R^2 = 0.07$, $\beta = -0.25$, $P = 0.033$) and males ($R^2 = 0.38$, $\beta = -0.25$, $P = 0.0089$). In the male model the density of psychiatrists, psychotherapists and GPs was also significant (not reported). Removing lithium levels as a predictor from the unweighted multivariate model reduced the proportion of the explained variance by 7.7%.

In the final weighted (WLS) multivariate model, lithium remained a significant predictor of SMRs (Table 2). The significance was marginal on male ($R^2 = 0.40$, $\beta = -0.19$, $P = 0.062$) and female SMRs ($R^2 = 0.07$, $\beta = -0.22$, $P = 0.088$). Removing lithium levels as a predictor from the WLS model reduced the proportion of the explained variance by 3.9%.

Both multivariate models (Table 2) were tested for multicollinearity. Tolerance values ranged between 0.187 and 0.811 and the highest condition index was 5.936, suggesting no multicollinearity. The Durbin–Watson test for autocorrelation revealed no autocorrelation of data.

Discussion

The results of this study indicate that lithium levels in drinking water are inversely associated with suicide rates and SMRs for suicide. We improved Ohgami *et al*'s model and replicated their findings of inverse association between suicide mortality and lithium levels in Oita prefecture on the basis of Austrian data. A strength of our study is that data on lithium concentrations were based on 6460 water measurements in comparison to 79.[8] Together with suicide SMRs, they were aggregated to 99 data-pairs – in contrast to 27 and 18 in previous studies.[7,8] Sensitivity analyses of the univariate models did not challenge the robustness of the findings. Also, adjustment for well-known socioeconomic confounders, which previously have been shown to be important predictors of suicide mortality in Austria,[11] did not affect the association with lithium concentrations in drinking water. The WLS procedure produced distortions of regression estimates especially in the separate gender analyses. The effects of lithium in drinking water on males and females were marginally significant. It has to be noted that the variables such as lithium levels, per capita income, proportion of Roman Catholics and the availability of mental health providers could not be stratified by gender for separate analyses, thus the estimates for both genders in our study and also in the Japanese study[8] are likely to be biased. Therefore marginal significance may be considered as a sign of robustness. Also, a further stratification of the data, for example by age groups, would lead to a further collapse of the power of the analysis due to decreasing cell counts per stratum.

Sources of lithium intake

Although it can be assumed that lithium in drinking water explains a part of the variance in suicide mortality, other possible lithium sources should be mentioned. Ohgami and colleagues[8] were criticised for having omitted consideration of individuals' intake of bottled mineral water,[9] which may contain high levels of lithium.[15] They were also criticised for not having accounted for the consumption of vegetables,[16] which absorb lithium from the soil and may be a complimentary lithium source.[4] For obvious reasons, data for both of these factors are not available at aggregate levels; hence we were unable to consider these factors. It has also been considered that lithium could play a role during the cooking process.[15] Indeed, lithium as a salt is likely to be taken up from drinking water into vegetables and animal-derived food and vice versa during osmotic processes. Lithium levels in food would then regress to the levels of local cooking/drinking water. A further source of lithium intake has not been mentioned in this discussion. It has not been considered before that tap water is also used for personal hygiene and it is known that lithium may be taken up percutaneously.[17] Therefore it needs to be considered whether the large water volumes used during bathing and showering could be an additional source of natural lithium. It is likely that transdermal and *per os* intake of lithium reflects local water lithium levels in Austria.

Lithium intake and excretion

It has been demonstrated that urinary excretion of lithium correlates with rainfall, due to a dilution effect of rainfall on ground water[18] and that urinary lithium levels correlate with lithium levels in drinking water and the amount of water consumed per day.[5] Lithium is absorbed via sodium channels in the small intestine and uniformly distributed in body water, although others have found differences in lithium levels between tissues[4] and plasma and brain concentrations.[19] Because renal clearance is not dependent on plasma lithium levels, plasma levels are proportional to daily intake.[20] Although excreted mainly by the kidney, approximately 80% of lithium is reabsorbed by the proximal renal tubule.[21] Excretion of lithium is dependent on the glomerular filtration rate and therefore affected by renal diseases and age, conditions in which plasma lithium increases. On the other hand, dehydration (and loss of salt) decreases the clearance of lithium.[19] These considerations suggest that water intake has at least a twofold effect on plasma lithium levels, and that lithium retention is probable when intake of water is reduced.

Estimated effects

Lithium concentrations in drinking water vary considerably by geographic region[4,5] and correlate with natural lithium resources. In northern Chile, a region with one of the largest lithium resources in the world located in the Salar de Atacama,[22] the natural concentrations of lithium in ground water may reach up to 5.2 mg/l, leading to a natural daily intake of lithium of up to 10 mg/day.[4,5] This is relatively high in comparison to the highest level of 1.3 mg/l measured in Austria. In our study, regional lithium concentrations explained only one part of the suicide mortality variance, namely up to 17% in the crude model and 3.9% in the adjusted and weighted model. Although the direction of the association and the significance of the statistical models were robust after sensitivity analyses and adjustment for confounders, the explained variance varied between the models. Adding variables to the multivariate models increased the total variance explained and suppressed the variance explained by lithium, although multicollinearity was absent. Finally, there is still considerable unexplained variance that is unaccounted for. It has to be noted that ecological studies *per se* are designed to establish hypotheses rather then proving cause, and their results are not applicable to individual cases (ecological fallacy). Thus, although informative, the estimates should be interpreted with caution due to the aggregated nature of data. In the crude model (online Fig. DS3), an increase of lithium concentration in drinking water by 0.01 mg/l was associated with a decrease in the suicide rate of 1.4 per 100 000 or a 7.2% reduction in the SMR for suicide. This would correspond to one conventional lithium pill (75 mg) in 7400 l (1955 gallons) of drinking water. Despite evolving evidence, the debate on whether continuous low-level lithium intake has protective effects on mental health and suicide risk should be further pursued. Although national suicide prevention programmes are increasingly implemented by politicians in many countries and researchers are seeking for effective preventive interventions,[23] it is a highly controversial question whether adding lithium to tap water would reduce suicide mortality as previously suggested.[24] It has to be noted that lithium concentrations increase in the brain during the first trimester of gestation[4] and early exposure to lithium may cause damage in human brain neurodevelopment.[25] Lithium acts on mood and suicidality via complex interactions with the serotoninergic system[26] and more recent studies suggest that lithium has stimulating effects on neurogenesis,[27] which could explain both toxicity during neurodevelopment as well as antidepressive/antisuicidal effects. Therefore, currently, not enough is known about the effects of natural lithium on the prevalence of neurodevelopmental disorders to consider artificially increasing its levels in drinking water as a method of universal prevention.

Implications

Owing to the sizeable magnitude of our finding, we provide conclusive evidence that lithium concentrations in drinking water are inversely correlated with suicide rates. Starting with anecdotic reports about the beneficial effects of lithium in drinking water on mental health in 1949 and earlier,[1] there is increasing evidence from three independent countries and continents that lithium in drinking water is associated with reduced mortality from suicide. In Texas, USA, lithium levels in drinking water were shown to be inversely associated with admissions and readmissions for psychoses, neuroses and personality disorders in state mental hospitals, as well as with homicide rates,[18,28] suicide and crime rates.[7] In Oita prefecture in Japan, lithium levels in tap water supplies were recently shown to be inversely associated with suicide mortality.[8] Of note, in 1969, lithium in drinking water was widely discussed as possibly having an impact on atherosclerotic heart disease[29,30] but this has not led to preventive supplementation of lithium in drinking water. Certainly, with these findings in mind, the true effects of chronic low-lithium intake on health and suicide should be investigated further.[31]

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First received 20 Dec 2010, final revision 31 Jan 2011, accepted 23 Feb 2011

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EXTRA CONTENT ONLINE

BJPsych | The British Journal of Psychiatry (2011)
198, 346–350. doi: 10.1192/bjp.bp.110.091041

Data supplement

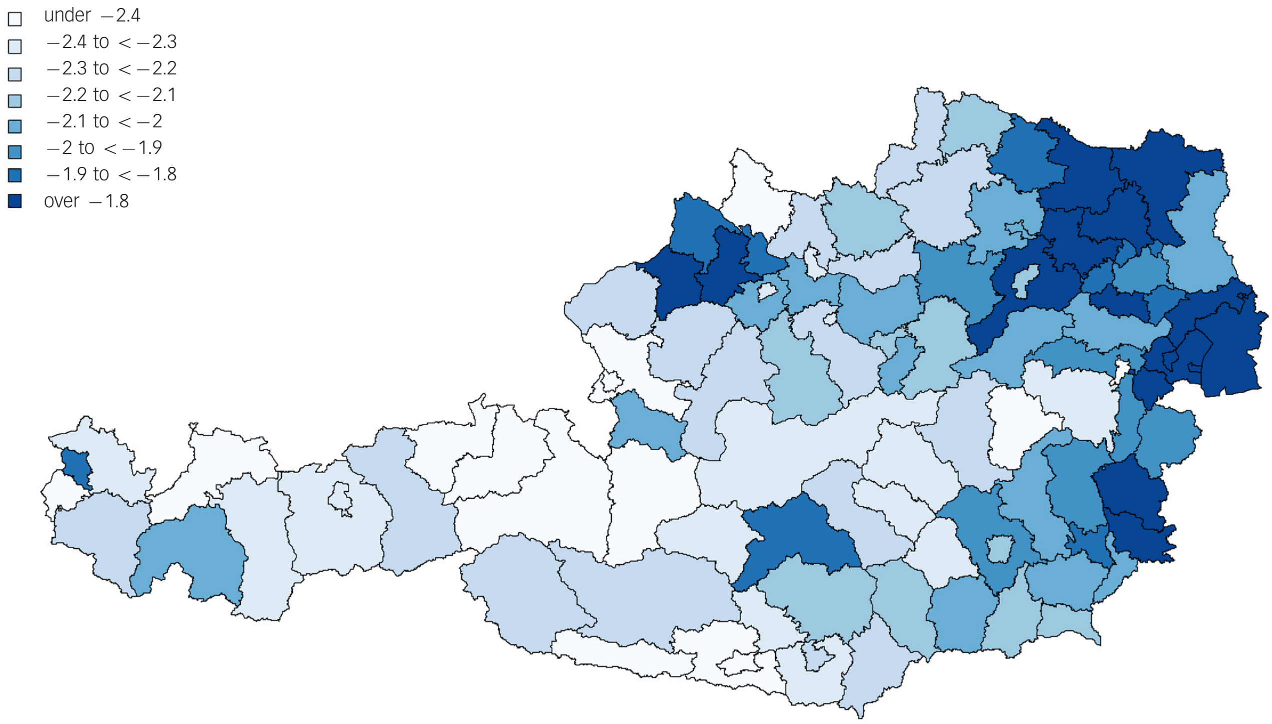

Fig. DS1 Logarithmised lithium levels in drinking water across 99 Austrian districts (2005–2010).

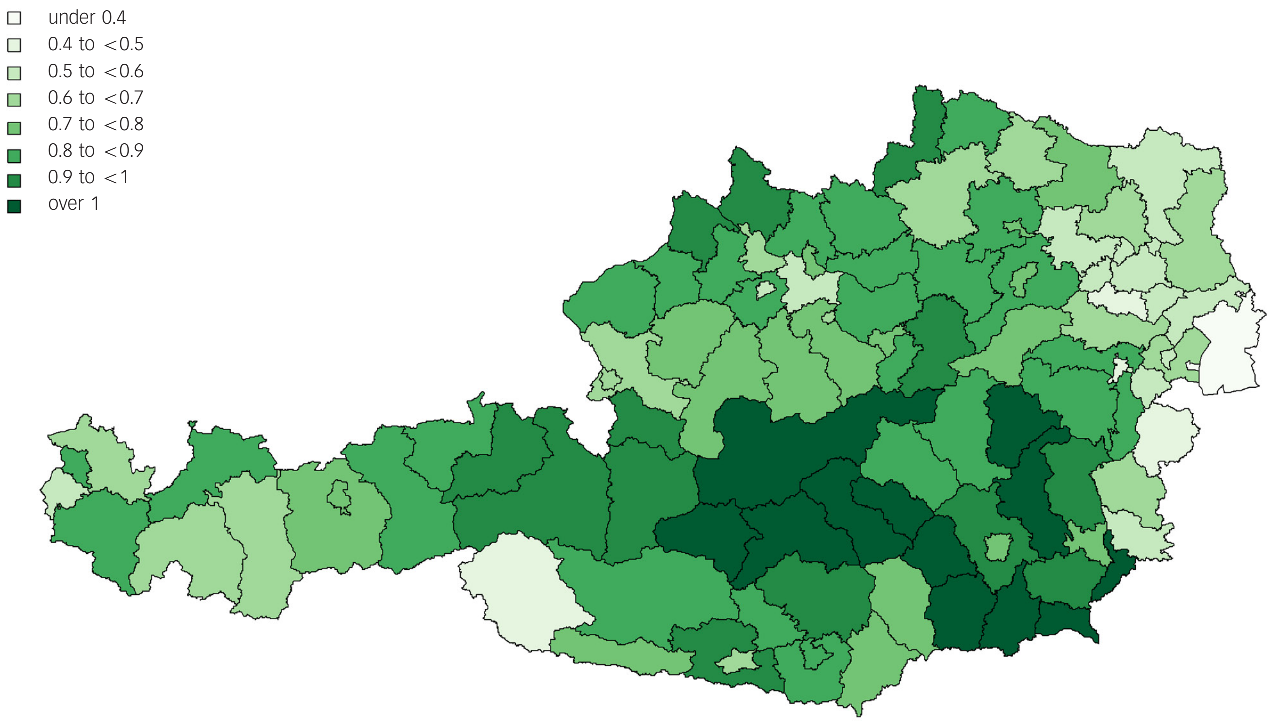

Fig. DS2 Standardised suicide mortality ratios across Austrian districts (2005–2009).

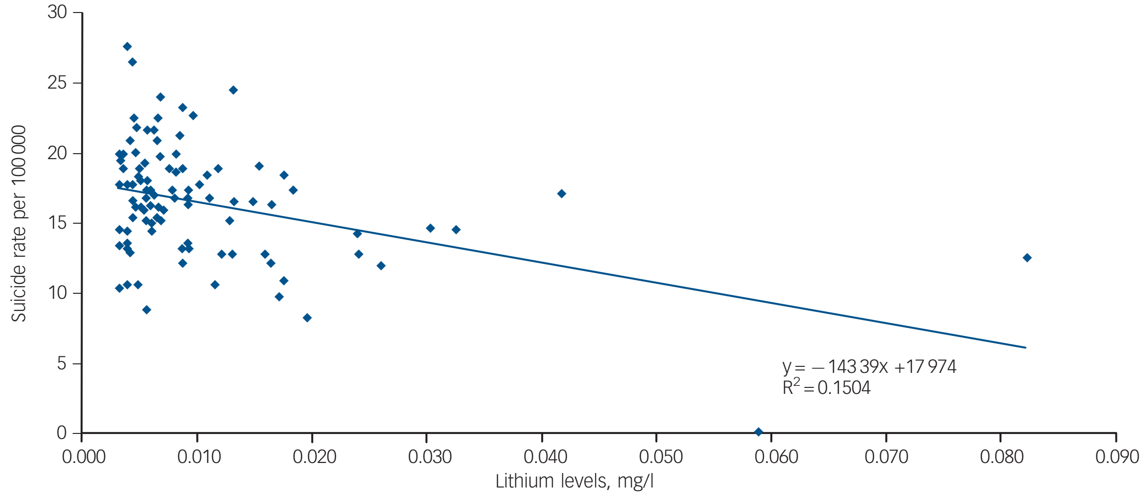

Fig. DS3 Crude lithium levels and suicide rates (2005–2009).

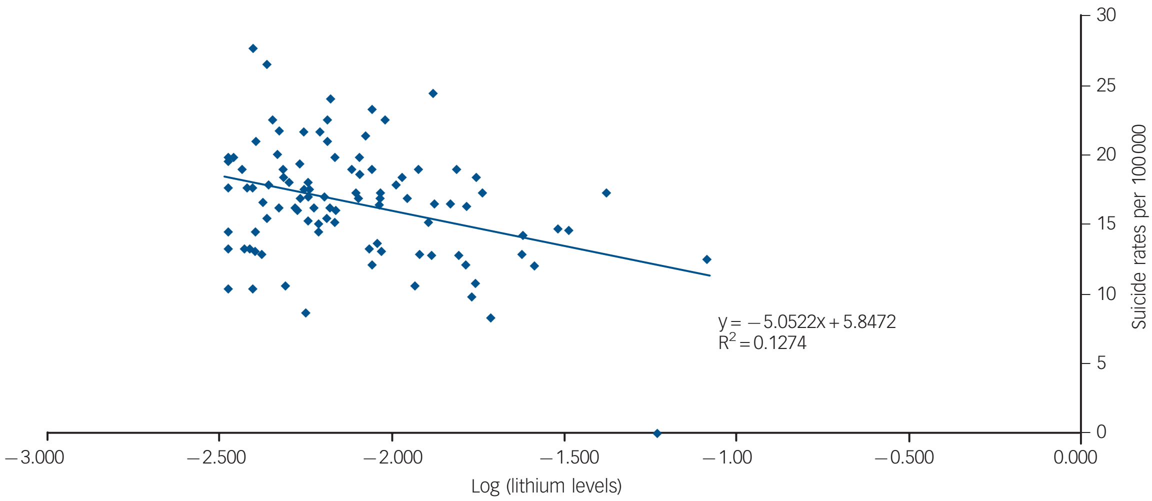

Fig. DS4 Log-transformed lithium levels and suicide rates (2005–2009).