Lithium in drinking water and suicide mortality: Interplay with lithium prescriptions

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Background
Little is known about the effects of lithium intake through drinking water on suicide. This intake originates either from natural rock and soil elution and/or accumulation of lithium-based pharmaceuticals in ground water.

Aims
To examine the interplay between natural lithium in drinking water, prescribed lithium-based pharmaceuticals and suicide in Austria.

Method
Spatial Bayesian regressions for males, females and pooled suicide mortality rates were estimated.

Results
Although the expected inverse association between lithium levels in drinking water and suicide mortality was confirmed for males and for total suicide rates, the relationship for females was not significant. The models do not indicate that lithium from prescriptions, assumed to accumulate in drinking water, is related to suicide risk patterns either as an individual effect or as a moderator of lithium levels in drinking water. Gender-specific differences in risk factors and local risk hot spots are confirmed.

Conclusions
The findings do not support the hypotheses that lithium prescriptions have measureable protective effects on suicide or that they interact with lithium in drinking water.

Declaration of interest
None.

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responsible for a non-random distribution of lithium in drinking water across regions. Although the findings discussed above have contributed significantly to our knowledge about the epidemiology of suicide, no research known to the authors deals with the relationship between prescribed lithium-based pharmaceuticals, natural lithium levels in drinking water and suicide mortality. In addition, gender differences are rarely considered separately, as higher and lower suicide rates tend to cluster spatially. Our study addresses these research gaps and focuses on the following research questions: (a) are lithium levels in drinking water associated with lithium prescriptions; (b) is there statistical evidence that any association found between suicide and lithium levels in drinking water is a function of lithium prescription rates operating as a moderating effect; and (c) are there gender-specific variations concerning both lithium-based variables (i.e. drinking water and lithium prescriptions) while controlling for other risk factors? To examine whether the natural lithium hypothesis holds true or whether the lithium levels in drinking water may result from the accumulation of lithium prescriptions in waste water (lithium prescription hypothesis), we generated the following hypotheses. First, districts with a high lithium level in drinking water also have high lithium prescription rates and both lithium sources are inversely associated with suicide rates, even when risk and protective factors are adjusted for. Second, natural lithium levels in drinking water have a suicide protective effect, even when adjusted for lithium prescriptions. Besides being vital for health prevention strategies, testing the lithium prescription hypothesis is of importance to medicine, public health and environmental science.

Study area

The empirical analysis was conducted in Austria using an ecological study design. Austria represents an excellent case study to explore the potential interaction between prescriptions rates and lithium in drinking water on suicide mortality. This is because of (a) its unique topography leading to different geological bedrocks and thus different natural lithium levels, (b) its alpine areas with reduced health service accessibility and (c) knowledge about the existence of essential confounding risk factors, therefore reducing the risk of an omitted variable bias. The study is based on 99 administrative territorial units (districts) from which suicide cases were available. In order to link the suicide numbers with prescription data available for each sanitation district, a few administrative districts were carefully aggregated to match the sanitation districts ($n=90$).

Data

The suicide data were collected from the Austrian mortality database, maintained by Statistics Austria (http://www.statistik.at/web_en/), on a case level. Suicide data comprise all registered suicides across all ages (with the youngest in the 5–9 age group and the oldest in 95+ age group) within the 5-year period from 2005 to 2009. In accordance with ICD-1029 the data include the following causes of death: poisoning (X60–X69), hanging (X70), drowning (X71), shooting (X72–X74), jumping (X80) and other less frequent causes of death (X75–X79, X81–X84). As suicide mortality is a rare event, the annual data were pooled over time to reduce the random fluctuations of suicides within a district. Moreover, because the raw number of suicides per district depends on the underlying population at risk, age and gender-adjusted standardised suicide mortality ratios (SMRs) were calculated. On average, the gender ratio in Austria is approximately 51% women and 49% men. The population counts extracted from the census of 2001 (Statistics Austria) serve as a baseline. The SMRs reflect the ratio between observed and expected suicides within each district. Mapping of the total SMR (SMRt) and gender-specific SMRs for males and females (SMRm, SMRf, respectively) in Fig. 1 indicate spatial heterogeneity in risk. Southern areas are faced with a more distinct risk compared with northeastern areas.

Besides suicide data, two other data-sets of prime interest were obtained, namely the lithium content in drinking water and lithium pharmaceuticals sales. Data about the former were provided by AQA GmbH (http://www.aqa-online.com) and came from 6460 water samples from across Austria. To merge the individual lithium measurements with the district-level data, the mean lithium concentration per district was computed and log transformed to a Gaussian-like distribution ($\log LITH$). On average the lithium content was 0.010 mg/L with a standard deviation of 0.010 mg/L. The lowest lithium level was 0.003 mg/L, whereas the highest was 0.016 mg/L than western parts (0.004 mg/L). As suicide mortality is a rare event, the annual data were pooled over time to reduce the random fluctuations of suicides within a district. Moreover, because the raw number of suicides per district depends on the underlying population at risk, age and gender-adjusted standardised suicide mortality ratios (SMRs) were calculated. On average, the gender ratio in Austria is approximately 51% women and 49% men. The population counts extracted from the census of 2001 (Statistics Austria) serve as a baseline. The SMRs reflect the ratio between observed and expected suicides within each district. Mapping of the total SMR (SMRt) and gender-specific SMRs for males and females (SMRm, SMRf, respectively) in Fig. 1 indicate spatial heterogeneity in risk. Southern areas are faced with a more distinct risk compared with northeastern areas.

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Dependent variable | Independent variable | Spearman’s $\rho$ | $P$  
--- | --- | --- | ---  
SMR, total | logLITH | $-0.370$ | $<0.001$  
SMR, total | logPHARM | $-0.290$ | $0.005$  
SMR, males | logLITH | $-0.320$ | $0.003$  
SMR, males | logPHARM | $-0.270$ | $0.010$  
SMR, females | logLITH | $-0.280$ | $0.009$  
SMR, females | logPHARM | $-0.040$ | $0.674$  
logLITH | logPHARM | $0.190$ | $0.076$  

SMR, suicide mortality ratio; logLITH, logged natural lithium in drinking water; logPHARM, logged lithium daily defined dose sold per km².
suicide mortality. Moreover, there is a tendency ($P<0.100$) that logLITH is positively associated with logPHARM.

To further explore the association between the lithium-based variables for different ranges of SMRs, conditional plots are shown in Fig. 3. Capital cities have high lithium prescription densities and function as leverage points dominating the regression line. In general, scatter plots indicate that logLITH and logPHARM were positively associated across different ranges of SMRs and gender. As logPHARM is much more pronounced in cities and thus distorts associations, it is mandatory to control for that issue. In this regard, population density seems to be a rational proxy variable. Figure 3(b), (d) and (f) show a slight tendency that in higher suicide risk areas the logLITH–logPHARM association is more positive than in lower risk areas. However, focusing on a specific SMR range reduces the sample size and results should be interpreted with caution.

Furthermore, to evaluate the spatial patterns of each variable, the Moran’s $I$ statistic with the five nearest neighbours were investigated ensuring that each district has a similar number of neighbours. Table 2 lists the results. The Moran’s $I$ statistic is highly significant for SMRt and the SMRm, indicating that similar values are located nearby. This finding is critical for subsequent analysis calling for a spatially explicit regression. Furthermore, Spearman correlations point to multicollinearity between some continuous risk factors requiring PCA to establish some uncorrelated principal components. The first three principal components, explaining in total approximately 84% of the overall variance, were selected for further analysis. (Principal component (PC)1 explains 58% of the variance, PC2 15%, and PC3 11%. In brief, the variables logPOPDENS, logINCOME, logPSYC, logPT and logGP load moderate negatively on PC1, whereas logUNEMPL loads lower negatively. In contrast, logROMCAT has a positive loading. LogUNEMPL possesses a negative loading on PC2, whereas other variables show minor positive or negative loadings. PC3 is mainly shaped by logGP and logROMCAT, which both having a strong positive loading.) Even though more difficult to interpret, these

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**Fig. 3** Conditional plots.  
Solid lines refer to a linear regression and dotted lines to a locally weighted polynomial regression. Suicide mortality ratios: (a) total, (b) total, without capital cities; (c) males, (d) males, without capital cities; (e) females and (f) females, without capital cities. Note (a), (c) and (e) are based on all data whereas (b), (d) and (f) do not consider data from eight provincial capital cities and Vienna. logPHARM, logged lithium daily defined dose sold per km²; logLITH, logged natural lithium in drinking water.
three PCs are used subsequently to adjust for confounding factors in the regressions.

To account for unmodelled residual patterns not explained by the three principal components, spatial Bayesian hierarchical models were estimated. In total, six models were run, namely two each for total, male and female. The modelling strategy comprises the following two models with rising complexity. First, individual effects of logLITH and logPHARM on SMRs were tested, while adjusting for a variety of risk factors included as principal components. These models are referred to as ‘model 1’. Second, the moderating effect of logPHARM on logLITH was tested by means of extending the previous model with a logLITH–logPHARM interaction term, representing ‘model 2’.

The deviance information criterion (DIC) serves for model comparison. A lower DIC score refers to a better fit. All models were set up on 100 000 MCMC samples, with 20 000 samples discarded during the burn-in period. To incorporate the geography, the models used a neighbourhood matrix based on the five nearest neighbours. Sensitivity runs, with a varying number of nearest neighbours, confirmed the robustness of the model specifications. All DIC scores suggest that models of type 1 rule out type 2 models. Residual independence was confirmed by the Moran’s I statistics, supporting the conclusion that spatial autocorrelations were captured appropriately. The posterior distributions of the fitted risk patterns of the best model, showing the anticipated negative sign, the models for SMR, and SMRm, of type 1 have positive logPHARM effects, which seem counterintuitive. However, neither for SMR nor for SMRm do the models support that these predictors are of relevance, as the 95% credible intervals include zero. In a similar study in France, regional prescription rates were negatively associated with male suicide.31

Models extended by logLITH–logPHARM moderating effects indicate that interactions were unrelated. This was also reflected in the weaker DIC scores. Furthermore, consideration of a lithium interaction effect in the three extended models 2 absorbed the significance of the originally important contribution of natural lithium, suggesting that logPHARM does not moderate the logLITH effect on suicide. Considerable gender differences were noticeable in the principal components controlling for potential confounders. Whereas the first and third principal components were relevant in modelling SMR, and SMRm, this conclusion was not supported by the SMR model. Not surprisingly this confirms the widely recognised fact of gender-specific risk factors as well as a generally lower female suicide risk. As indicated by regional dummies, evidence exists that suicide rates vary within Austria at a region-wide scale. Compared with southern areas, i.e. Carinthia and Styria, the other regions have a considerably lower suicide risk. This conclusion is valid throughout the models. In addition, small-scale suicide spill-over effects beyond regions were present, efficiently captured by all models. The p parameter indicates that complete suicide patterns cannot be explained by confounders alone. This mirrors previous findings emphasising that geography is a crucial factor in explaining suicide patterns.

Finally, the estimated suicide risks, represented as the posterior distributions of the fitted risk patterns of the best performing models (model 1), are illustrated in Fig. 4. Although a general comparison suggests similar risk patterns, a detailed inspection indicates striking differences across space and between

### Table 2 Moran’s I results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Moran’s I</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMR, total</td>
<td>0.414</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SMR, males</td>
<td>0.386</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SMR, females</td>
<td>0.057</td>
<td>0.104</td>
</tr>
<tr>
<td>logLITH</td>
<td>0.539</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>logPHARM</td>
<td>0.083</td>
<td>0.059</td>
</tr>
</tbody>
</table>

SMR, suicide mortality ratio; logLITH, logged natural lithium in drinking water; logPHARM, logged lithium daily defined dose sold per km².

Model 1 provides considerable evidence that logLITH has the expected negative influence on suicide. This holds true for the total suicide ratio and for males. This means that higher natural lithium levels decrease the suicide risk. This inverse association is in line with previous studies. Even though the sign of the coefficient for females matches the results for SMR, and SMRm, statistical significance was not reached. However, for prescription rates (logPHARM), a contradictory result in comparison with the bivariate correlations was found. With the exception of the SMR model, showing the anticipated negative sign, the models for SMR, and SMRm, of type 1 have positive logPHARM effects, which seem counterintuitive. However, neither for SMR nor for SMRm, do the models support that these predictors are of relevance, as the 95% credible intervals include zero. In a similar study in France, regional prescription rates were negatively associated with male suicide.31

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Finally, the estimated suicide risks, represented as the posterior distributions of the fitted risk patterns of the best performing models (model 1), are illustrated in Fig. 4. Although a general comparison suggests similar risk patterns, a detailed inspection indicates striking differences across space and between

### Table 3 Results of the estimated models for suicide mortality ratio, total

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median</th>
<th>2.5%</th>
<th>97.5%</th>
<th>P</th>
<th>Median</th>
<th>2.5%</th>
<th>97.5%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.483a</td>
<td>0.144</td>
<td>0.827</td>
<td></td>
<td>0.441</td>
<td>0.212</td>
<td>1.113</td>
<td></td>
</tr>
<tr>
<td>logLITH</td>
<td>-0.080a</td>
<td>-0.136</td>
<td>-0.024</td>
<td></td>
<td>-0.088</td>
<td>-0.214</td>
<td>0.041</td>
<td></td>
</tr>
<tr>
<td>logPHARM</td>
<td>0.015</td>
<td>-0.002</td>
<td>0.062</td>
<td></td>
<td>0.029</td>
<td>-0.176</td>
<td>0.226</td>
<td></td>
</tr>
<tr>
<td>logLITH × logPHARM</td>
<td>0.003</td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
<td>-0.038</td>
<td>0.042</td>
<td></td>
</tr>
<tr>
<td>PC1</td>
<td>0.035a</td>
<td>0.004</td>
<td>0.065</td>
<td></td>
<td>0.035a</td>
<td>0.004</td>
<td>0.065</td>
<td></td>
</tr>
<tr>
<td>PC2</td>
<td>0.022</td>
<td>-0.009</td>
<td>0.052</td>
<td></td>
<td>0.021</td>
<td>-0.009</td>
<td>0.052</td>
<td></td>
</tr>
<tr>
<td>PC3</td>
<td>0.025a</td>
<td>0.018</td>
<td>0.085</td>
<td></td>
<td>0.052a</td>
<td>0.019</td>
<td>0.084</td>
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<tr>
<td>RegEAST</td>
<td>-0.188a</td>
<td>-0.322</td>
<td>-0.063</td>
<td></td>
<td>-0.190a</td>
<td>-0.328</td>
<td>-0.066</td>
<td></td>
</tr>
<tr>
<td>RegMD</td>
<td>-0.147a</td>
<td>-0.248</td>
<td>-0.042</td>
<td></td>
<td>-0.147a</td>
<td>-0.240</td>
<td>-0.039</td>
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<tr>
<td>RegWEST</td>
<td>-0.147a</td>
<td>-0.250</td>
<td>-0.038</td>
<td></td>
<td>-0.147a</td>
<td>-0.247</td>
<td>-0.036</td>
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<tr>
<td>ρ</td>
<td>0.370a</td>
<td>0.040</td>
<td>0.860</td>
<td></td>
<td>0.390a</td>
<td>0.050</td>
<td>0.870</td>
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<tr>
<td>DIC</td>
<td>-190</td>
<td></td>
<td></td>
<td></td>
<td>-186</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Moran’s I errors</td>
<td>-0.019</td>
<td>0.537</td>
<td>-0.013</td>
<td></td>
<td>0.488</td>
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</table>

logLITH, logged natural lithium in drinking water; logPHARM, logged lithium daily defined dose sold per km²; PC1, first principal component; PC2, second principal component; PC3, third principal component; Reg, regional dummy variable; MD, central area of Austria; DIC, deviance information criterion.

a. There is strong evidence that this variable is relevant.
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Main findings

The objective of this study was to test the hypothesis whether pharmaceutical lithium prescriptions accumulating in ground-water together with natural lithium in drinking water jointly affect suicide mortality. Utilising spatial Bayesian hierarchical models we looked for this potential co-association in 99 districts in Austria. Although correlation analyses confirm that both natural lithium in drinking water and prescription rates are inversely associated with suicide and both lithium sources are weakly and positively associated, these conclusions are reversed, as soon as risk factors are adjusted for. This may also explain why prior studies using a bivariate research design have reported non-significant results regarding suicide and natural lithium levels. More importantly, the models in our study do not support the lithium prescription hypothesis. Both, for total and gender-specific suicide mortalities no evidence was found that lithium-based pharmaceuticals either directly or via accumulation in drinking water diminish the risk of death by suicide. Neither the individual effects nor the lithium interaction effect turned out to be significant when adjusted for confounders, suggesting that lithium in drinking water does not seem to originate from lithium-based pharmaceutical medications (i.e. Quilonorm, Neurolepsin) used in psychiatric treatments. This conclusion is independent of SMR stratification and consistent throughout the models providing additional support that suicide and lithium levels in drinking water are not a function of lithium prescription rates across Austria. However, natural lithium levels in drinking water still provide an explanation for the spatial distribution of suicide mortality. For both the total suicide rates and the male-specific rates the suicide-protective property of natural lithium is confirmed, with a stronger negative effect for males. This outcome corroborates previous studies and emphasises the validity of the natural lithium hypothesis stating that lithium in drinking water likely originates from natural sources.

Our results also verify that suicide risk varies considerably across Austria, as indicated by the regional dummy variables that were consistently significant, even after carefully modelling suicide

genders. This impression is also confirmed by a correlation analysis between risk surfaces. A high correlation exists between the total risk and the risk for males with a Spearman’s ρ of 0.970 (P < 0.001). However, the total risk is lower when correlated with the female risk (ρ = 0.730, P < 0.001) and the correlation between male and female is even lower (ρ = 0.610), although highly significant (P < 0.001). It is apparent that suicide risk varies significantly across Austria. All risk surfaces show a rough trend of elevated risks from the north to the south with a more pronounced overall risk in the federal state of Styria, which has risk values above 1. Independently of this risk pattern, the Styrian district Voitsberg has, in particular, a distinctly elevated suicide risk. For that district the total risk is 1.142, which is even more significant than the northern Burgenland, including the north-eastern areas, including the central area of Austria; DIC, deviance information criterion.

Table 4 Results of the estimated models for gender-specific suicide mortality ratios

<table>
<thead>
<tr>
<th></th>
<th>Model 1: without interaction effect</th>
<th>Model 2: with interaction effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>2.5%</td>
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<tr>
<td>Males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>0.416^a</td>
<td>0.024</td>
</tr>
<tr>
<td>logLITH</td>
<td>-0.092^a</td>
<td>-0.157</td>
</tr>
<tr>
<td>logPHARM</td>
<td>0.026</td>
<td>-0.029</td>
</tr>
<tr>
<td>logLITH × logPHARM</td>
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<td></td>
</tr>
<tr>
<td>PC1</td>
<td>0.049^a</td>
<td>0.012</td>
</tr>
<tr>
<td>PC2</td>
<td>0.017</td>
<td>-0.020</td>
</tr>
<tr>
<td>PC3</td>
<td>0.051^a</td>
<td>0.012</td>
</tr>
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<td>RegEAST</td>
<td>-0.221^a</td>
<td>-0.361</td>
</tr>
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<td>RegMID</td>
<td>-0.161^a</td>
<td>-0.273</td>
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</tr>
<tr>
<td>p</td>
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<td>0.030</td>
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<td>DIC</td>
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<tr>
<td>Moran’s I errors</td>
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<td>Females</td>
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<td>Intercept</td>
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<td>RegMID</td>
<td>-0.106</td>
<td>-0.273</td>
</tr>
<tr>
<td>RegWEST</td>
<td>-0.245^a</td>
<td>-0.421</td>
</tr>
<tr>
<td>p</td>
<td>0.350^a</td>
<td>0.010</td>
</tr>
<tr>
<td>DIC</td>
<td>-19</td>
<td></td>
</tr>
<tr>
<td>Moran’s I errors</td>
<td>-0.119</td>
<td></td>
</tr>
</tbody>
</table>

logLITH, logged natural lithium in drinking water; logPHARM, logged lithium daily defined dose sold per km²; PC1, first principal component; PC2, second principal component; PC3, third principal component; Reg, regional dummy variable; MD, central area of Austria; DIC, deviance information criterion.

a. There is strong evidence that this variable is relevant.

Discussion

The objective of this study was to test the hypothesis whether pharmaceutical lithium prescriptions accumulating in ground-water together with natural lithium in drinking water jointly affect suicide mortality. Utilising spatial Bayesian hierarchical models we looked for this potential co-association in 99 districts in Austria. Although correlation analyses confirm that both natural lithium in drinking water and prescription rates are inversely associated with suicide and both lithium sources are weakly and positively associated, these conclusions are reversed, as soon as risk factors are adjusted for. This may also explain why prior studies using a bivariate research design have reported non-significant results regarding suicide and natural lithium levels. More importantly, the models in our study do not support the lithium prescription hypothesis. Both, for total and gender-specific suicide mortalities no evidence was found that lithium-based pharmaceuticals either directly or via accumulation in drinking water diminish the risk of death by suicide. Neither the individual effects nor the lithium interaction effect turned out to be significant when adjusted for confounders, suggesting that lithium in drinking water does not seem to originate from lithium-based pharmaceutical medications (i.e. Quilonorm, Neurolepsin) used in psychiatric treatments. This conclusion is independent of SMR stratification and consistent throughout the models providing additional support that suicide and lithium levels in drinking water are not a function of lithium prescription rates across Austria. However, natural lithium levels in drinking water still provide an explanation for the spatial distribution of suicide mortality. For both the total suicide rates and the male-specific rates the suicide-protective property of natural lithium is confirmed, with a stronger negative effect for males. This outcome corroborates previous studies and emphasises the validity of the natural lithium hypothesis stating that lithium in drinking water likely originates from natural sources.

Our results also verify that suicide risk varies considerably across Austria, as indicated by the regional dummy variables that were consistently significant, even after carefully modelling suicide
spill-over effects from adjacent districts through a spatial Bayesian model formulation. This supports findings from Hungary that showed that suicides are geographically agglomerated. Compared with women, men are at greater risk of dying by suicide; this risk is evidently increased in the southern regions of Austria. In contrast, lowest risk exists in the north-east of Austria. This implies that suicide prevention strategies and programmes must reflect gender dissimilarities and local circumstances in risk patterns by providing specific localised health intervention strategies, such as reducing suicide risk factors and improving protective factors related to mental health well-being.

**Strengths and limitations**

By extending previous ecological lithium–suicide studies with the additional of a rational alternative lithium source, namely lithium prescription rates, our study adds to the literature. Besides controlling for a rich set of socioeconomic risk factors and confounding effects of access to health services, a key strength of the study is the larger sample size (of 99 districts) compared with most previous studies. Another major strength is the statistically sound analysis design, explicitly accounting for local suicide spill-over effects while simultaneously controlling for regional heterogeneity in suicide risk. However, some limitations can be identified. In contrast to cohort studies on an individual level, the present models are cross-sectional and based on ecological regression. Thus, the district-related findings do not allow us to draw conclusions about individuals. Even though the utilised risk and protective factors successfully absorb confounding effects, a few variables could be further stratified by age and/or gender, which might have an impact on the model. Finally, lithium intake via nutrition is not taken into account, which might also contribute to daily lithium exposure.

Despite these reservations, the statistically significant inversely related association between lithium in drinking water and suicide support the validity of the natural lithium hypothesis. No evidence for lithium-based pharmaceutical medication effects on suicide could be confirmed, either as a direct effect or as a moderating effect via natural lithium in drinking water. It is likely, that in comparison with other psychopharmacological prescriptions such as antidepressants, lithium prescriptions have only a minimal relieving effect on the nations burden of mental disease. Therefore spatial analysis of antidepressant prescriptions on suicide rates, such as that presented by Gibbons et al., should be considered for further research.

**Fig. 4** Estimated suicide risk.

Suicide mortality ratios (a) total, (b) males and (c) females. Dark grey lines delimit federal states, light grey lines define sanitation district boundaries.

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**References**


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