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Lithium in the public water supply and suicide mortality in Texas

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ABSTRACT

There is increasing evidence from ecological studies that lithium levels in drinking water are inversely associated with suicide mortality. Previous studies of this association were criticized for using inadequate statistical methods and neglecting socioeconomic confounders. This study evaluated the association between lithium levels in the public water supply and county-based suicide rates in Texas. A state-wide sample of 3123 lithium measurements in the public water supply was examined relative to suicide rates in 226 Texas counties. Linear and Poisson regression models were adjusted for socioeconomic factors in estimating the association. Lithium levels in the public water supply were negatively associated with suicide rates in most statistical analyses. The findings provide confirmatory evidence that higher lithium levels in the public drinking water are associated with lower suicide rates. This association needs clarification through examination of possible neurobiological effects of low natural lithium doses.

1. Introduction

The positive effects of lithium on mood and mental health were first described in the late 1940s (Cade, 1949). Lithium has since been widely used as a first-line treatment for bipolar disorder, and as an augmentation treatment for unipolar depressive disorder (Bauer et al., 2006). The suicide-protective properties of lithium in therapeutic dosages for treating bipolar (Baldessarini et al., 2006; Goodwin et al., 2003) and major depressive disorder (Baldessarini et al., 2003; Guzzetta et al., 2007) are well established.

There is growing evidence from ecological studies that lithium traces in ground and drinking water may protect against suicide. A negative association between lithium concentrations in the municipal water supply and suicide rates was first reported for 27 Texas counties (Schrauzer and Shrestha, 1990). This finding was affirmed in the Oita prefecture in Japan (Ohgami et al., 2009). Several methodological concerns were raised about these results regarding the used statistical methods (Huthwaite and Stanley, 2010) and the failure of the investigators to adjust for possible socioeconomic factors that influence suicide rates (Chandra and Babu, 2009).

A study conducted in the East of England, using separate measurements of lithium for 47 subdivisions, found no correlation between lithium levels in tap water and suicide rates (Kabacs et al., 2011). A nationwide Austrian study, however, which used 6460 lithium measurements from 99 districts, found an inverse correlation between lithium concentrations in drinking water and suicide rates (Kapusta et al., 2011). Well-known socioeconomic determinants of suicide were adjusted for in the analysis. In a subsequent commentary on that study, use of more appropriate statistical methods was recommended for validation purposes for future research (Yang, 2011).

This current study incorporates salient socioeconomic determinants of suicide and employs pertinent statistical procedures in revisiting the research question on a nexus between lithium levels in drinking water and suicide rates. Our geographic focus was the area where the association was first documented, namely Texas (Schrauzer and Shrestha 1990). In performing both linear and Poisson regression analyses, using more recent data for a very large set of Texas counties, we adjusted for various potential socioeconomic confounders and utilized a large number of water samples.

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2. Methods

2.1. Data acquisition

Applying public health informatics techniques, we linked data abstracted from three sources: the Texas Department of State Health, the US Census Bureau, and the Texas Water Development Board Groundwater Database. We retrieved the most recent (1999–2007) crude and age-adjusted suicide mortality rates per 100,000 for 254 Texas counties from the Texas Department of Health (http://soupfin.tdh.state.tx.us/deathdoc.htm), which are based on a subset of variables drawn from the Texas Certificate of Death. These data were linked, using the primary key of county and/or county code, to Texas population detailed data derived from census and intercensal estimates of populations by age for Texas counties (http://www.dshs.state.tx.us/chs/popdat/detailX.shtm), and county population density data from the US Census Bureau for 2000 (http://factfinder.census.gov). Using data from the American Community Survey for 2007, we also obtained the respective prevalence of females, African Americans, Hispanic and Latino Americans, as well as median income per household, and poverty and unemployment rates by county. Finally, we linked lithium levels from the Texas Water Development Board Groundwater Database (http://www.twdb.state.tx.us). Water sample data were collected between 1999 and 2007. In total, 3123 water samples from public wells, analysed for dissolved lithium levels, were accessed and averaged for 226 counties. Mean lithium levels in the Texas counties ranged between 2.8 and 219.0 μg/l (0.000403 and 0.0315 mmol/l).

2.2. Statistics

Public health informatics facilitates the use of publicly available data for understanding health outcomes through the secondary use of routinely collected data. The complexity of data integration is largely dependent on the research question and data sources (Zhang, 2012). For our study, we considered each county as an independent unit, with all data representing the county level. Our information permitted deterministic data linkage. The Texas Department of State Health reports both crude and age-adjusted rates, adjusted to the 2000 U.S. population, but does not permit disaggregation for age-adjusted rate regression modelling. In addressing this data limitation, we compared our linear and Poisson regression results.

We modelled the response of county-level rate of suicide in Texas, using both a linear and a Poisson rate regression adjusted for county-based population density, lithium levels, age, gender, race/ethnicity, median income per household, and poverty and unemployment rates. Both statistical approaches were generalized linear models with respective identity and log link functions. For these data, the crude suicide rate was an analytically reasonable surrogate for the age-adjusted rate. Both rates were highly correlated ($R^2 = 0.92$) with a standard deviation of the error term of 1.65 suicides per 100,000. For both regressions, we expected that the estimated regression coefficients would be unbiased but less efficient. Thus, we projected that the estimated coefficients would be an accurate measure of the association between the lithium levels and suicide rates, but that the standard error would be larger due to the increased variance from our use of crude rather than age-adjusted rates (Carroll et al., 2006; Gustafson, 2004).

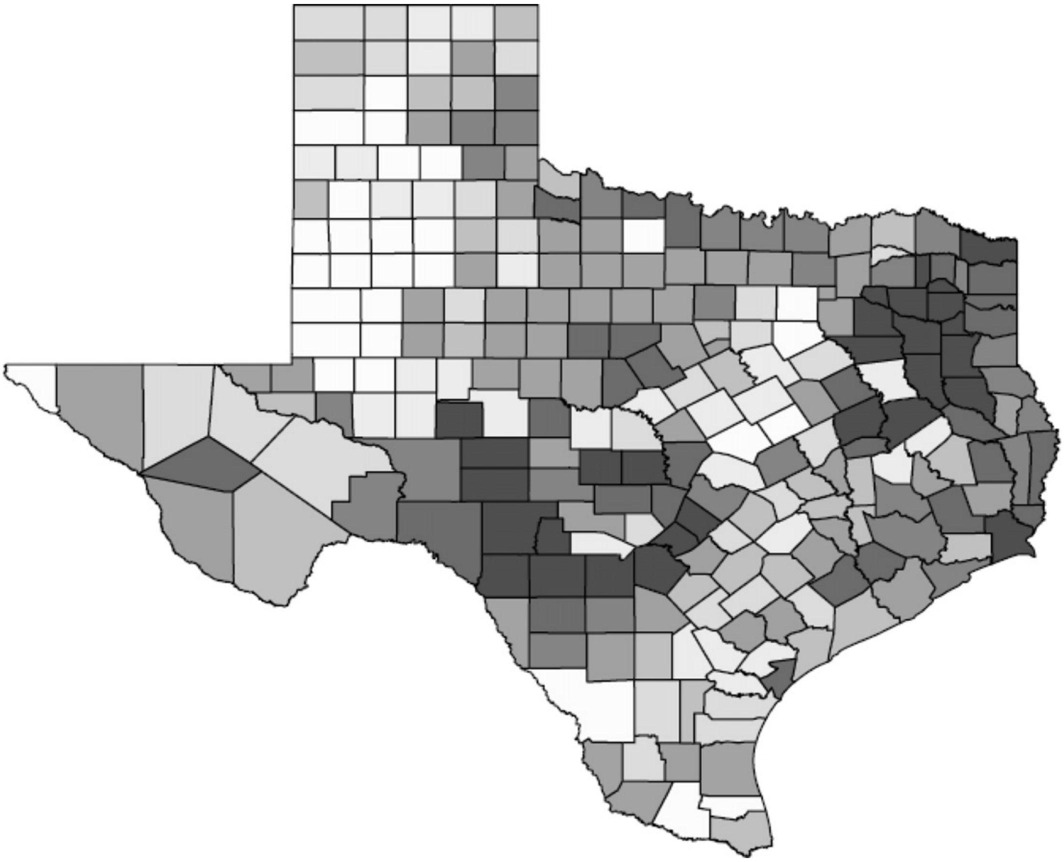

Fig. 1. Average lithium levels in Texas, 1999–2007 (darker areas represent lower levels).

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With the crude suicide rate serving as a very good surrogate for the age-adjusted rate, with no anticipated impact on the bias of the estimates, we used Poisson rate regression with a log link function to characterize suicide rates in Texas counties by demographic variables and lithium prevalence. We transformed the dependent variable, crude rate, using $R^* = f(R^c, \alpha_0, \gamma) = n/[p^\gamma \exp(\alpha_0)]$, where n is the number of suicides in a county over the nine-year period, p is the aggregate population for a county over the same period, α_0 is the intercept for the rate regression model on the log scale, and γ indexes the county population. We performed the Poisson regression, as previously described, using R^* as our response. The transformation of the crude rate adjusts the rate for underlying county size, while retaining an interpretation of the coefficients as a rate ratio.

In order to capture the non-linearity of the data, we permitted fractional polynomial transformations for all independent variables. Using degree 2 multivariable fractional polynomial transformations, we combined transformation selection with closed test, deviance-based model selection, while maintaining a family-wise Type I error rate of 0.1. To ensure numerical convergence of the algorithm, we restricted the fractional polynomial of the percentage of females in a county to be degree 1.

A sensitivity analysis was performed to consider alternate generalized linear models and the effect of analytically identified influential counties. To increase model comparability, we reported the results from this sensitivity analysis on the coefficient scale, with corresponding 95% confidence intervals reported on the rate ratio scale. We used the statistical computing environment R version 2.14.1 for our data analyses (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

The geographical distributions of $SR_{adj.}$ and lithium levels for our selected set of Texas counties are illustrated in Figs. 1 and 2.

We considered linear regression, weighted linear regression for adjusted rates, Poisson rate regression using the crude rate as a surrogate for the age-adjusted rate, and quasi-Poisson regression on the age-adjusted rates. In assessing model adherence to the underlying assumptions for each modelling strategy, we determined that the optimal approach was Poisson rate regression using fractional polynomial transformation. Moreover, this model was suitable because the underlying assumption, that the data were generated from a stochastic rate process, aligned with the Poisson process model of data generation. Finally, we did not use the multinomial characterization of the age distribution for each county in our Poisson regression, due to recurring problems with multicollinearity and our capacity to employ a good surrogate for the desired age-adjusted response.

Table 1 shows the results from the best fit model for a linear regression, with a square root transformed response and fractional polynomial transformations for all covariates, and a weighted linear regression with analyst-chosen transformations for the covariates. Lithium levels were only significantly associated with age-adjusted suicide rates in the weighted model.

For the Poisson rate regression (Table 2), we investigated three models; a naïve rate regression using the crude rate with no covariate transformations, a rate regression with fractional polynomials with all analytically identified influence and leverage counties removed, and a weighted quasi-Poisson regression for the adjusted suicide rate with analyst-chosen variable transformations. Mean lithium levels were

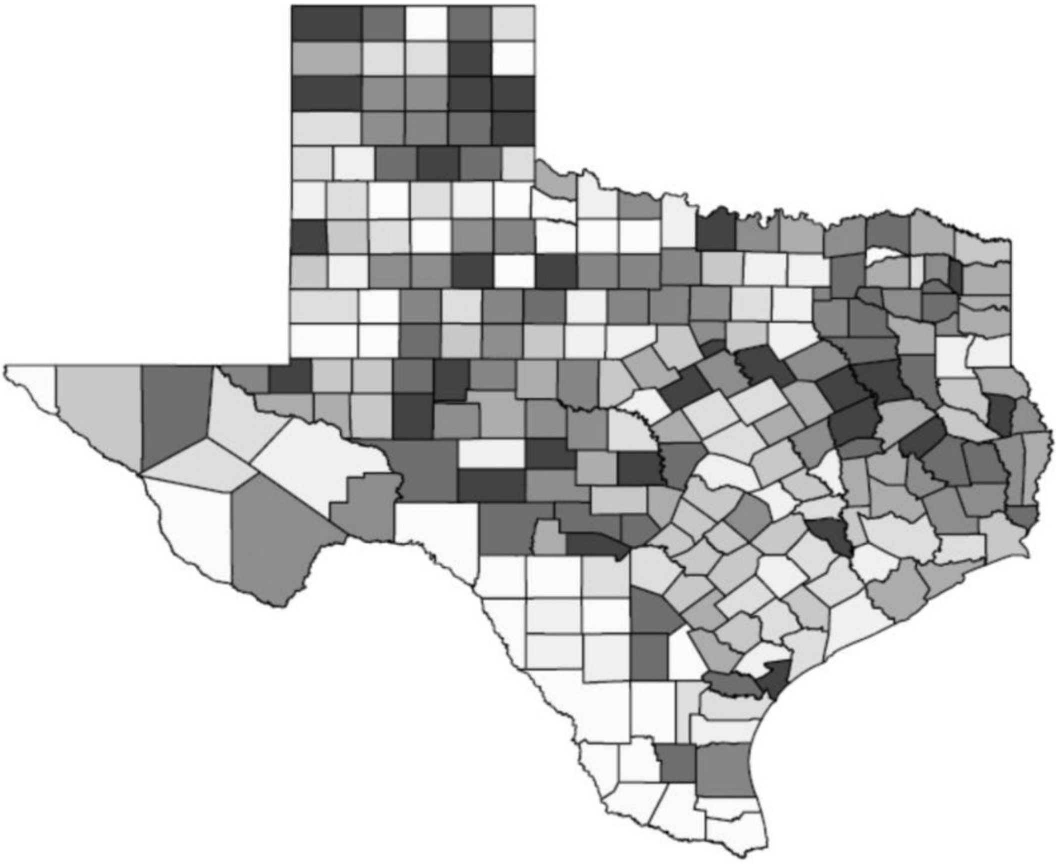

Fig. 2. Annualised suicide rates ($SR_{adj.}$) in Texas, 1999–2007 (darker areas represent higher $SR_{adj.}$).

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Table 1
Linear regression sensitivity analysis to transformations and subset selection for adherence to model assumptions (estimated coefficients are given with standard error in brackets).

Model	Linear regression with transformed response and fractional polynomials[a]	Weighted linear regression[b]
Characteristic		
Intercept	3.75 (0.08)***	−7.05 (0.47)***
Log lithium level		−0.04 (0.02)**
Proportion Hispanics/10	−0.13 (0.02)***	
Log proportion Hispanics		−0.15 (0.03)***
Log unemployment		−0.4 (0.09)***
Log population density		−0.06 (0.01)***
(Population density/100)$^{-0.5}$	0.07 (0.02)***	
Sqrt proportion African Americans		0.04 (0.02)*

**p*-value < 0.05, ***p*-value < 0.01, ****p*-value < 0.001.

[a] Foard, Hansford King, Sterling, and Stonewall counties removed as influence points.

[b] Transformations chosen by analyst with King County removed as outlier.

statistically significant in all Poisson models (rate ratio for fractional polynomial model: 0.88 for 100 μg/l; 95% CI: 0.84, 0.93). Table 3 shows the suicide rate ratio as a function of the change in the mean lithium level for the Poisson regression model with fractional polynomials.

In a subsequent sensitivity analysis, we calculated a Poisson rate regression model with fractional polynomials and a single extreme outlier removed. This model used two lithium terms, lithium divided by 100, and the square of the scaled lithium term. Both terms were statistically significant, but with different directions: lithium level/100: −0.27 (0.05), (lithium level/100)^2: 0.13 (0.03).

A typical implementation of a Poisson rate regression sets the offset coefficient to one, whereas our transformation required the estimation of the offset coefficient, γ. Table 2 indicates that the proposed transformation of the crude rate resulted in a log population offset, with a coefficient of (0.94, SE 0.01). Although not statistically equivalent to one, it captured the correct magnitude and direction. We further observed that the fractional polynomial model rescaled the independent variables to a common magnitude.

4. Discussion

Our study provides further evidence that lithium levels in the public water supply in Texas are negatively associated with suicide mortality rates at the county level. Utilizing more appropriate statistical procedures and a more recent time period, this research agrees with the findings of a study conducted in Texas during the 1970–1980s (Schrauzer and Shrestha, 1990), and also those from studies conducted in Austria (Kapusta et al., 2011) and the Oita prefecture in Japan (Ohgami et al., 2009).

Lithium levels in Texas public water ranged between 2.8 and 219 μg/l (0.000403 and 0.0315 mmol/l), and are significantly lower than those found in some regions with large natural lithium concentrations (Schrauzer, 2002). However, they are markedly higher than the levels reported for an East of England study (range: <1–21 μg/l) that found no association (Kabacs et al., 2011). The investigators in that study argued that the narrow range of the lithium concentrations could potentially explain their null findings on the association between lithium levels and suicide rates.

A strength of our study is that lithium concentrations were based on 3123 lithium measurements with a range of 1–331 measures per county. Assuming that the measured lithium values oscillate about the true lithium value for the county, much like blood pressure measurements oscillate about the true blood pressure, and that the random noise causing this oscillation is normally distributed (e.g. $N\{0, \sigma\}$), then the use of the average county lithium level is a reasonable estimate, in expectation, of the true county lithium value. We linked the lithium data with the age-adjusted suicide rate for each of the 226 Texas counties comprising our dataset. This dataset made our study the largest to examine the association between lithium concentrations in drinking water and suicide rates. We used Poisson regression models, as well as linear models, in order to address statistical criticisms of prior research (Huthwaite and Stanley, 2010; Yang, 2011). The negative association between lithium levels and suicide rates remained significant, even after we adjusted for important socioeconomic determinants of suicide in the models (Chandra and Babu, 2009; Kapusta et al., 2010). Applying advanced models, we found that the negative correlation between

Table 2
Poisson regression sensitivity analysis to transformations and subset selection for adherence to model assumptions (estimated coefficients are given with standard error in brackets).

Model	Poisson rate regression, naïve[a]	Poisson rate regression with fractional polynomials[b]	Weighted quasi-Poisson regression[c]
Characteristic			
Intercept	−8.09 (0.11)***	−7.35 (0.20)***	4.27 (0.44)***
Log population		0.94 (0.01)***	
Lithium level	-<0.01 (<0.01)***		
Log lithium level			−0.04 (0.01)*
(Lithium level/100)		−0.12 (0.03)***	
Log population density			−0.05 (0.01)***
(Population density/100)$^{-1}$		0.01 (0.002)***	
(Population density/100)$^{-0.5}$		−0.14 (0.03)***	
Proportion African Americans	−0.01 (<0.01)***		
Sqrt proportion African Americans			0.03 (0.01)*
(Proportion African Americans + 0.1)/10		−0.10 (0.02)***	
Proportion Hispanics	−0.01 (<0.01)***		
Log proportion Hispanics			−0.13 (0.02)***
(Proportion Hispanics/10)^2		−0.01 (<0.01)***	
Log unemployment			−0.39 (0.08)***
(Unemployment/10)$^{-2}$		−0.14 (0.05)**	
(Unemployment/10)$^{-2}$ × log (Unemployment/10)		−0.09 (0.03)***	
Median household income	−<0.01 (<0.01)***		
(Median Household Income/100,000)^3		−1.15 (0.09)***	

**p*-value < 0.05, ***p*-value < 0.01, ****p*-value < 0.001.

[a] Anderson, Bee, Bexar, Brazoria, Brazos, Cameron, Collin, Denton, Ector, El Paso, Galveston, Hidalgo, Montgomery, Nueces, Potter, Sabine, Tarrant, Walker, Webb, and Williamson counties removed as influence points.

[b] Anderson, Callahan, Dallam, Delta, Eastland, Ellis, Henderson, Swisher, Washington, Willacy, and Zavala counties removed as influence and leverage points.

[c] Transformations chosen by analyst with King County removed as outlier due to preliminary analysis of the data.

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Table 3
Suicide rate ratio as a function of the change in the mean lithium level for the Poisson rate regression model with fractional polynomials.

Increase in mean lithium level (µg/l)	10 µg/l	20 µg/l	30 µg/l	40 µg/l	50 µg/l	60 µg/l	70 µg/l	80 µg/l	90 µg/l	100 µg/l
All levels	0.99	0.98	0.96	0.95	0.94	0.93	0.92	0.91	0.90	0.88
95% CI	(0.98,0.99)	(0.97,0.99)	(0.95,0.98)	(0.93,0.97)	(0.92,0.96)	(0.90,0.96)	(0.89,0.95)	(0.87,0.94)	(0.85,0.94)	(0.84,0.93)

lithium levels and suicide rates remained significant. While affirming the hypothesis, this association is weak and susceptible to differences in statistical approaches. For example, when we used linear regression, lithium was only significantly associated with suicide rates in population-weighted models. Also, the additionally calculated Poisson regression model, with only one outlier removed, showed the fragility of the linear inverse association between lithium levels and suicide rates. Thus, any protective effect of naturally occurring lithium in the water supply may be small to moderate.

Despite methodological improvements over prior studies, our study has at least two limitations. One is substantive and the other methodological. First, we could not factor in dietary sources of lithium uptake beyond public drinking water. These sources include bottled mineral water (Huthwaite and Stanley, 2010), and vegetables, grains, and spices (Chandra and Babu, 2009; Desai and Chaturvedi, 2009; Schrauzer, 2002). Other potential confounding factors are varying lithium prescription rates across different counties, which hypothetically could influence lithium levels in drinking water. Secondly, ecological studies serve to generate hypotheses rather than permit causal inference. Consequently, our results need to be interpreted with caution.

While there is accumulating evidence that high lithium levels in drinking water may protect against suicide, a call for supplementing drinking water with lithium would be premature. More research is needed to understand how tap-water lithium impacts thyroid function, pregnant women, and foetuses *in utero* (Chandra and Babu, 2009; Kapusta et al., 2011). Nonetheless, our results highlight a need for further evaluation of the relationship between chronic low-lithium intake, suicide, and other health outcomes, such as the prevalence of Alzheimer's disease. Given multiple confirmatory ecological studies, randomized controlled trials and designed analytic observational studies will be necessary to further our understanding about the relationship between low-level lithium intake and suicide. Even if such subsequent studies also suggest a protective effect, before water supplementation could be justified, there will be a need for corroborative evidence from in-depth investigations of the neurobiological mechanisms of potential antisuicidal and other properties of lithium.

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None.

Contributors

Nestor Kapusta, Ian Rockett, and Victor Blüml designed the study and wrote the protocol. Benjamin Vyssoki, Victor Blüml, and Tom Bschor managed the literature searches and analyses. Michael D. Regier, Gerald Hlavin, and Franz König undertook the statistical analysis. Nestor Kapusta and Victor Blüml wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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