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ORIGINAL INVESTIGATION

Relationships of local lithium concentrations in drinking water to regional suicide rates in Italy

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Abstract

Objectives. Higher natural concentrations of lithium in drinking water may be associated with lower local rates of suicide. *Methods*. Lithium concentrations in drinking water were assayed by mass spectrometry at 145 sites in Italy, and compared with reported local suicide rates for men and women between 1980 and 2011. *Results*. Lithium concentrations in drinking water averaged 5.28 [CI: 4.08–6.48] μg/L (0.761 [0.588–0.934] μEq/L) and ranged from 0.110 to 60.8 μg/L (1.58 to 8.76 μEq/L). Lithium concentrations and local suicide rates were not significantly inversely related, except in 1980–1989, particularly among women. *Conclusions*. A proposed association between trace lithium concentrations in drinking water and risk of suicide was only partially supported, and mechanisms for potential clinical effects of trace levels of lithium are unknown.

Key words: *suicide, lithium, quality of life, mood stabilizers, affective disorders*

Introduction

Suicide is a major public health challenge, accounting for approximately 800,000 deaths annually worldwide (WHO 2014). Suicide rates vary greatly among countries and regions within countries. Efforts to develop effective and practicable methods for suicide prevention are leading priorities worldwide. Only recently have medicinal treatments been associated with reduced rates of suicidal behaviour (Meltzer et al. 2003; Baldessarini et al. 2006; Tondo and Baldessarini 2014). In 2003, clozapine use in schizophrenia became the first and only treatment given regulatory recognition for antisuicidal effects (Meltzer et al. 2003; Tondo and Baldessarini 2015). Lithium also may have antisuicidal actions, and is rare in having quite consistent evidence of substantial reductions of rates of suicides and potentially fatal attempts in several placebo-controlled trials and when used long-term at clinical doses by mood disorder patients, particularly those with bipolar disorder (Baldessarini et al. 2006; Baldessarini 2013). This effect may or may not be a manifestation of overall clinical improvement, reflect selective actions on behavioural states associated with suicide, or

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related, at least in part, to close supervision typical of the clinical use of lithium (Ahrens and Müller-Oerlinghausen 2001; Baldessarini 2013; Manchia et al. 2013; Tondo and Baldessarini 2015).

The evident antisuicidal effect of clinical treatment with lithium makes several reports of possible associations between higher natural trace concentrations of lithium in drinking water with lower local rates of suicide in different countries (including Austria, Greece, Japan, and the USA), particularly interesting (Schrauzer and Shrestha 1990; Ohgami et al. 2009; Kapusta et al. 2011; Blüml et al. 2013; Giotakos et al. 2013; Vita et al. 2015). Sugawara et al. (2013) in Japan found an association between higher concentrations of lithium in drinking water and lower suicide rates only among women, whereas Blüml et al. (2013) in Texas found such an association only when a specific statistical model was used, and a lack of association was reported by Kabacs et al. (2011) in England. The inconsistent findings in these reports may reflect the low natural abundance of lithium in drinking water in most regions and small quantities in foodstuffs. Such concentrations average three orders of magnitude below doses of lithium salts and lithium plasma concentrations used clinically to treat patients with mood disorders (μEq/L vs. mEq/L) (Baldessarini 2013). On the other hand, biological and clinical effects of even trace concentrations sustained over many years might occur.

Approximately 4000 suicides are reported each year in Italy, with great regional variation. Northern regions and Sardinia report the highest rates (Masocco et al. 2010; Vichi et al. 2010; Pompili et al. 2011, 2014). These variations encourage consideration of the hypothesis that there may be an inverse correlation between suicide rates and local concentrations of lithium in drinking water. Guided by findings in cited reports, we addressed three major questions: (1) to what extent does the local concentration of lithium in tapwater correlate with local suicide rates; (2) do such associations remain stable over time; and (3) are there differences in the hypothesized association between women and men or by population density, geographic location, or altitude? The primary study hypothesis was that Italian regions and communities with relatively high natural concentrations of lithium in drinking water have lower suicide rates.

Methods

Study sample

We analysed data from 145 sites at which samples of drinking water in public distribution systems were assayed for lithium concentrations. Sampling included communities of varied sizes, ranging from the smallest town of Cutigliano in Tuscany (population 1,561) to the largest city of Rome (population 2.6 million), and all Italian cities with more than 500,000 inhabitants, to account for 29% (17.2 million) of the total Italian population of 59.4 million (59.7% females). Data on local population sizes and suicide rates were provided by the Italian National Institute of Statistics (ISTAT; Ferrara 2009).

Measurement of lithium concentrations in tapwater

A total of 157 water samples were collected in 2009–2010 within the framework of a research program aimed at characterizing the geochemistry of natural and bottled water (Reimann and Birke 2010), subsequently integrated with additional samples (Dinelli et al. 2012a), to represent a total of 145 Italian communities. Lithium concentrations were assayed with an Agilent Technologies Corporation (Santa Clara, CA) inductively coupled plasma quadropole mass spectrometry (ICP-QMS) 7500ce instrument, under clean room conditions at the Bundesanstalt für Geowissenschaften und Rohstoffe (BGR) Laboratories in Hannover Germany (Birke et al. 2010). The analytical detection limit for lithium ion (atomic weight = 6.94) was 10 ng/L (1.44 nEq/L), and the precision (coefficient of variation: standard deviation [SD]/mean) of repeat assays from independent samples from the same water supply averaged 0.451 [95% CI: 0.156–0.746]. The distribution of lithium concentrations in tapwater was considerably skewed toward higher concentrations (skewness $\pm$ SD = 3.90 $\pm$ 0.20; kurtosis $\pm$ SD = 23.0 $\pm$ 0.40). Log-transformed concentration improved normalization (skewness = –0.24; kurtosis = –0.45) and was used for the reported analyses.

Suicide data

Information on suicide mortality was extracted from the ISTAT Mortality Database, which includes data from all death certificates of Italian citizens who die in Italy, and codes causes of death according to the World Health Organization International Classification of Diseases ([ICD-9 or -10]; WHO 1987, 2003), specifically considering ICD-9 categories E950–E959 and ICD-10 categories X60–X84 and X87.0 (WHO 2014). Computerized mortality data were available for all years from 1980 to 2011, except for 2004 and 2005.

Annual average suicide rates per 100,000 population were computed at the municipality level for each site providing data on lithium concentrations in local drinking water. Suicide rates were standardized by age and sex to the 2001 Italian population according to the direct method (Minelli et al. 2010). As suicide in Italy is very uncommon under age 15, rates were computed for ages ≥ 15 years. Suicide mortality rates (per 100,000 person-years) were computed for men and women separately, for three periods: 1980–1989, 1990–1999, 2000–2011. Local Standardized Mortality Ratios (SMRs) for suicide were computed for each study community, comparing the observed number of deaths with the corresponding expected figures derived from Italian national rates (Minelli et al. 2010) to allow comparisons with previously reported findings. These computations were based on PATED.4.3 (Procedure for the Spatial Analysis of Descriptive Epidemiology) software (Qin 2005).

Statistical analyses

Based on lithium concentrations and suicide data analysed at the community level, we compared Pearson's correlation coefficients (r) with one-tailed tests (as positive associations of lithium concentration and suicide rate were not found in previous studies), and modelled the associations by linear regression. Because population size varied widely among the sampled communities, we used weighted least-squares (WLS) linear regression modelling to test the association of lithium level in drinking water and suicide rates, weighted for local population size. In a basic model, we included only the lithium level as predictor variable for suicide rate. In multivariable regression models, we included the following covariates: (a) totally mountainous area as defined by ISTAT (Istituto Nazionale di Statistica 2014), (b) highly urbanized (population density of ≥ 500 inhabitants/km^2 and total local population ≥ 50,000), and (c) geographic location south of Rome, as these factors had been reported previously to be associated with suicide rates (Qin 2005; Vichi et al. 2010; Helbich et al. 2012; Young 2013). Data on these covariates at the municipality level were extracted from the *Atlante Statistico dei Comuni* (ASC version3.0) (Ferrara 2009).

Analyses were performed for site-specific populations over age 15 years, and for men and women separately, stratifying by three time periods (1980–1989, 1990–1999, 2000–2011). Analyses employed commercial statistical software IBM-SPSS.21 (IBM-SPSS Corp., Chicago, IL). Statistical outcomes were considered "possibly significant" at one-tailed $P = 0.05–0.10$, "significant" at $P = 0.05–0.01$, and "highly significant" at $P < 0.01$.

Results

For communities ($n = 9$) providing more than one water sample (1.08 samples/community, overall) lithium concentrations in local drinking water were averaged. Averaged values (five from Naples, two from other multi-sampled sites) ranked (mean ± SD, μg/L): Matera (5.43 ± 0.47), Forlì (4.75 ± 2.82), Ravenna (4.64 ± 3.92), Naples (4.61 ± 3.71), Urbino (3.65 ± 1.58), Taranto (3.22 ± 0.28), Turin (1.62 ± 0.16), Genoa (1.25 ± 1.30), and Venice (0.81 ± 0.06). Lithium concentrations across the 145 sampled Italian sites ranged from a minimum of 0.11 μg/L (1.58 nEq/L) at Pordenone in Northeast Italy, to a highest level of 60.8 μg/L (8.76 μEq/L) at Quarrata in Tuscany in Central Italy. Overall, lithium concentration averaged 5.28 [CI: 4.08–6.48] μg/L (0.761 [CI: 0.588–0.934] μEq/L; Figure 1).

These concentrations indicate an approximate daily intake of lithium of 2.3 μEq (0.76 μEq/L × 3 L/day). By comparison, a typical clinical daily dose of lithium carbonate (MW = 73.9 g/mol) for clinical use to treat bipolar disorder is 900 mg, containing 12.2 mmol or 22.4 mEq of lithium, or 9739-times (22,400/2.3 μEq) more than from drinking water. Moreover, typical clinical plasma concentrations of lithium are approximately 0.75 mEq/L, or 987-times (750/0.76 μEq/L) less than the average concentration of lithium in Italian drinking water.

For data available between 2000 and 2011, the mean, standardized national suicide rate averaged 7.53 [CI: 7.45–7.61] per 100,000 population/year. In the same period, 11,222 suicide deaths were reported in the 145 study sites (29.0% of the national total, or the same as the proportion of the national population, at 17.2/59.4 millions), and the standardized suicide rate across the study sites averaged 7.15 [CI: 7.01–7.28]/100,000/year, similar to the national average. Among sampled sites, the highest suicide rate (33.4/100,000/year) was found at Cutigliano in Tuscany, where the lithium concentration in drinking water was 2.61 μg/L, a relatively low value. Of note, there were no suicide deaths reported in Caronia in Sicily, with a relatively high lithium concentration (15.2 μg/L), but also not at Sant'Agata Feltria in northeastern Italy, where the lithium concentration (1.66 μg/L) was far below the national average of 7.15 μg/L. As predicted, the overall suicide rate was significantly associated with location in mountainous regions, highly urbanized communities, and at sites south of Rome. In addition, there was a significant, overall secular decrease in suicide rates at the study sites, between 1980 and 2011 (by –1.73 [–2.24 to –1.22] %/year, which was somewhat greater among women (–2.67 [–3.23 to –2.11]) than men (–1.53 [–2.92 to –0.11] %/year; see Supplemental material available online at http://dx.doi.org/10.3109/15622975.2015.1062551).

Overall, lithium concentrations in tapwater and local suicide rates were not statistically significantly correlated by unweighted linear correlation (Table I).

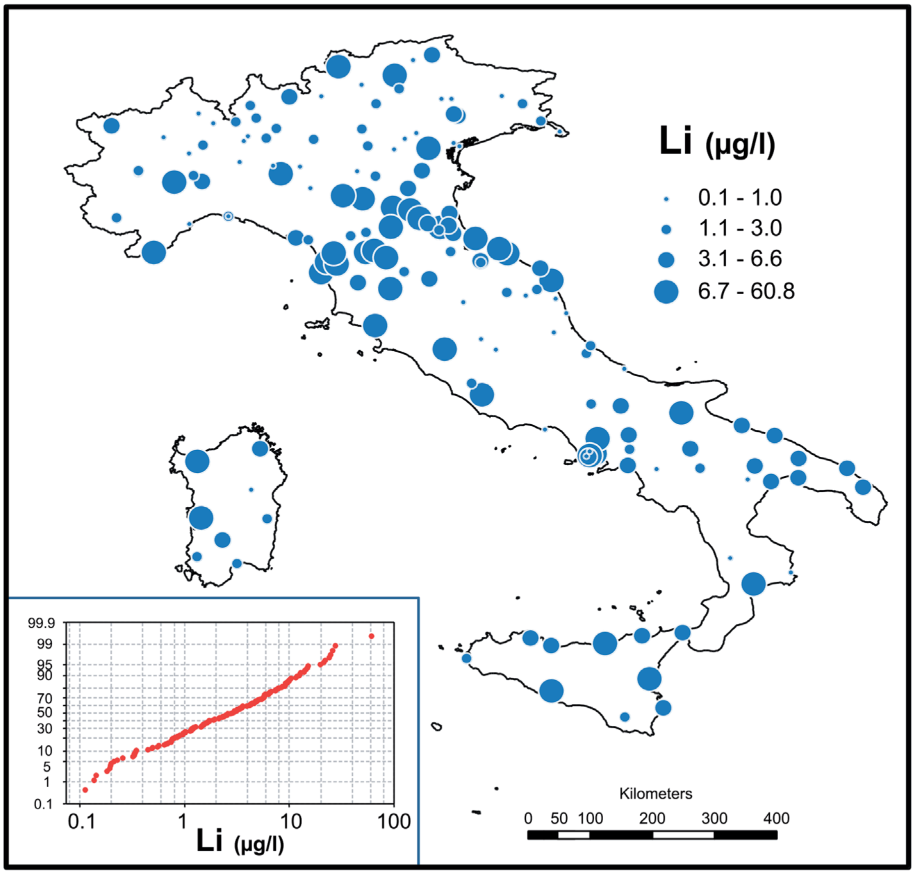

Figure 1. Symbols are proportional to lithium concentrations, in quartiles.

Nevertheless, a possibly significant correlation between suicide rate and lithium concentration was found selectively among women in the period 1980–1989, among whom the relationship was negative (less suicide with more lithium), as hypothesized, but weak ($r = -0.125$; $P = 0.07$; Table I).

Table I. Pearson correlation (unweighted) between local characteristics and standardized mortality rates for suicide among men and women in decades between 1980 and 2011.

	Standardized annual suicide rate					
	Overall		Male		Female	
Characteristics	*r*	*P* value	*r*	*P* value	*r*	*P* value
			1980–1989			
Lithium	–0.081	0.168	–0.030	0.361	**–0.125**	0.066
Mountainous	**+0.158**	0.029	**+0.138**	0.049	+0.037	0.331
High urbanized	**–0.116**	0.083	**–0.139**	0.048	+0.30	0.358
South Italy	**–0.342**	<0.001	**–0.312**	<0.001	**–0.251**	0.001
			1990–1999			
Lithium	–0.099	0.119	–0.099	0.118	–0.051	0.272
Mountainous	**+0.309**	<0.001	**+0.317**	<0.001	+0.033	0.347
High urbanized	**–0.201**	0.008	**–0.191**	0.011	–0.050	0.275
South Italy	**–0.396**	<0.001	**–0.331**	<0.001	**–0.310**	<0.001
			2000–2011			
Lithium	–0.039	0.321	–0.019	0.410	–0.009	0.455
Mountainous	**+0.415**	<0.001	**+0.413**	<0.001	+0.710	0.397
High urbanized	**–0.274**	<0.001	**–0.262**	0.001	–0.075	0.185
South Italy	**–0.359**	<0.001	**–0.293**	<0.001	**–0.300**	<0.001

Based on weighted least-squares univariate regression modelling, lithium concentrations were significantly negatively associated with overall suicide rates (women and men), only in 1980–1989 (β = –0.231, $P = 0.005$; Table II, Figure 2). Among men, there was a weak negative association, again only for 1980–1989 (β = –0.139, $P = 0.095$; Table II). However, among women, there was a significant negative association across all three-study decades (Table III).

Multivariate modeling also was adjusted for highly urbanized areas, location south of Rome, and in mountainous areas – all factors that have been associated with higher suicide rates (Qin 2005; Vichi et al. 2010; Helbich et al. 2012; Young 2013) but were not related to lithium in water supplies in the present study (all $r \leq 0.13$, all $P \geq 0.14$). The association between lithium concentration and suicide rate was statistically significant only for females, and only for the period 1980–1989 (β = –0.153, $P = 0.042$; Table II).

Findings remained substantially unchanged when the analyses were based on Standardized Mortality Rates (SMRs: observed in the local area/expected, based on Italian national rates as reference; Minelli et al. 2010) for each study community for the three study periods (1980–1989, 1990–1999, 2000–2011) to allow comparisons with previously reported findings. These results are provided in appended, supplementary material.

Discussion

Based on previous studies of natural lithium concentrations in drinking water reviewed above (Vita et al. 2015) and on evidence that clinical treatment with lithium carbonate is associated with lower rates of suicide and life-threatening attempts (Baldessarini et al. 2006; Vita et al. 2015), the present study tested the hypothesis that higher concentrations of lithium in tapwater are associated with lower reported local suicide rates. We also considered men and women separately, compared three decades between 1980 and 2011, and included covariates reported to be associated with suicide rates in Italy. Overall, the findings did not support a consistent inverse relationship of lithium concentration and suicide rate.

However, such a relationship was found selectively for women, particularly in the 1980s. Also, based on weighted least-squares, bivariate regression modelling, lithium concentrations were significantly negatively associated with overall suicide rates (in women and men), but only in 1980–1989 (Table I). In addition, based on multivariate modelling that considered local population density, higher geological altitude, and locales south of Rome – all previously

Table II. Standardized suicide rates and lithium levels in drinking water, based on weighted least-square regression modelling.

Model	Dependent variable	Independent variables	Total Slope β	Total *P* value	Total Adjusted r^2	Men Slope β	Men *P* value	Men Adjusted r^2	Women Slope β	Women *P* value	Women Adjusted r^2
Crude model 1.1	Average total standardized suicide rate (1980–1989)	Lithium	**–0.231**	0.005	+0.047	**–0.139**	0.095	+0.012	**–0.342**	<0.001	+0.110
Adjusted model 1.2	Average total standardized suicide rate (1980–1989)	Lithium	–0.033	0.656	+0.339	+0.050	0.495	+0.326	**–0.153**	0.042	+0.295
		Mountainous	+0.048	0.490		+0.013	0.850		+0.035	0.628	
		Urbanized	–0.008	0.911		–0.090	.0210		**+0.163**	0.025	
		South Italy	**–0.581**	<0.001		**–0.592**	<0.001		**–0.478**	<0.001	
Crude model 2.1	Average total standardized suicide rate (1990–1999)	Lithium	–0.055	0.511	–0.004	+0.009	0.918	–0.007	**–0.187**	0.024	+0.028
Adjusted model 2.2	Average total standardized suicide rate (1990–1999)	Lithium	+0.075	0.348	+0.205	+0.114	0.159	+0.200	–0.023	0.780	+0.193
		Mountainous	+0.102	0.187		+0.098	0.204		+0.033	0.667	
		Urbanized	**–0.139**	0.076		**–0.209**	0.008		+0.086	0.272	
		South Italy	**–0.448**	<0.001		**–0.406**	<0.001		**–0.446**	<0.001	
Crude model 3.1	Average total standardized suicide rate (2000–2011)	Lithium	–0.029	0.725	–0.006	+0.036	0.670	–0.006	**–0.170**	0.041	+0.022
Adjusted model 3.2	Average total standardized suicide rate (2000–2011)	Lithium	+0.049	0.527	+0.252	+0.103	0.177	+0.282	–0.069	0.409	+0.140
		Mountainous	**+0.141**	0.060		**+0.170**	0.021		+0.006	0.945	
		Urbanized	**–0.303**	<0.001		**–0.338**	<0.001		–0.122	0.133	
		South Italy	**–0.374**	<0.001		**–0.357**	<0.001		**–0.360**	<0.001	

Measures with P-values <0.10 are in bold.

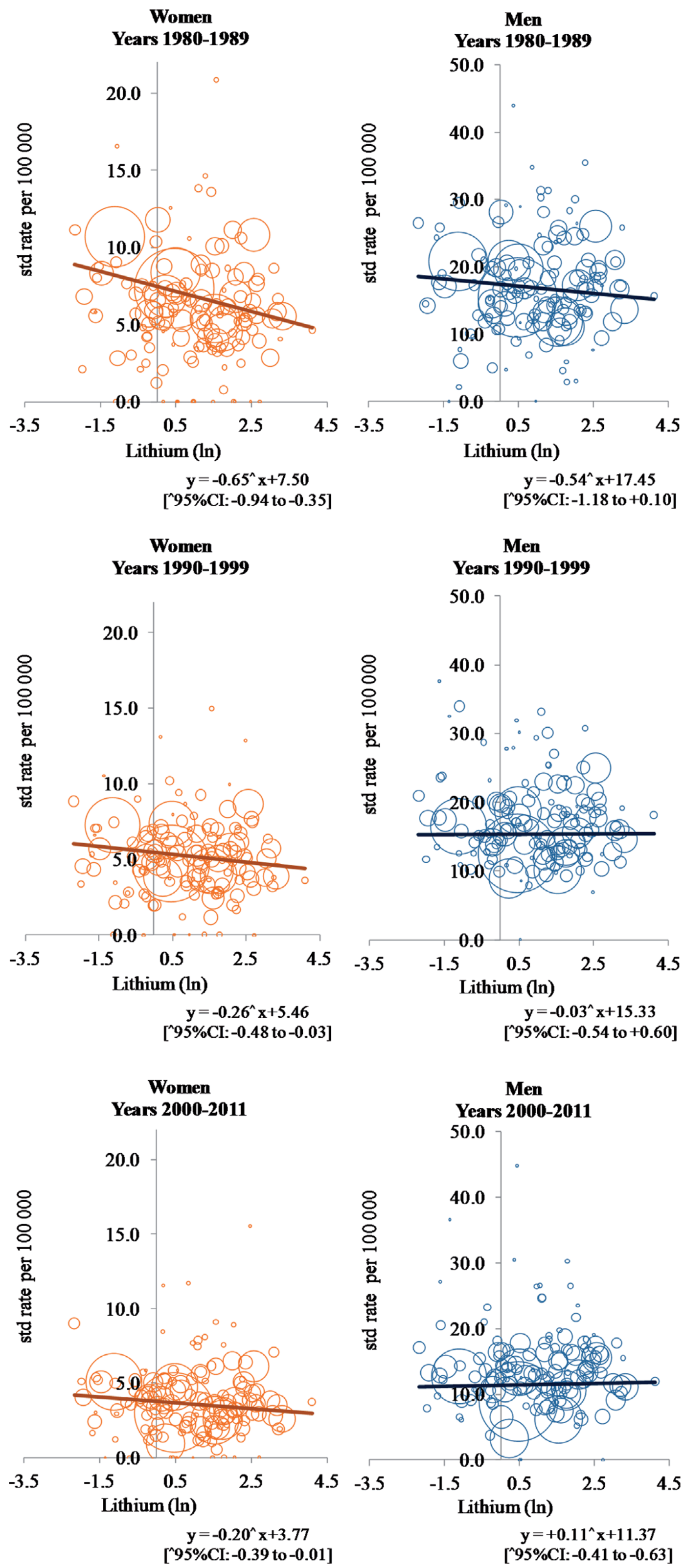

Figure 2. Lithium concentration is log-transformed and circle-size is proportional to local population-size. Analysis is based on weighted least-squares linear regression modelling.

found to be associated with suicide rates in Italy (Qin 2005; Vichi et al. 2010; Helbich et al. 2012; Young 2013) – in addition to lithium concentration in local water supplies, there was again a significant negative association for women for the 1980s only (Table II). Among men, there was a weak negative, bivariate

Table III. Standardized suicide rates in regions of lowest versus highest lithium concentrations.

Years	Suicide rates [95% CI] Lowest lithium (0.11–1.02 μg/L)	Highest lithium (6.56–60.8 μg/L)	*T* score	*P* value
Total				
1980–1989	12.7 [12.3–13.1]	11.8 [11.3–12.2]	1.17	0.247
1990–1999	10.6 [10.2–10.9]	10.8 [10.5–11.2]	0.26	0.800
2000–2011	8.0 [7.60–8.20]	8.3 [8.00–8.60]	0.52	0.603
Men				
1980–1989	18.9 [18.1–19.8]	18.6 [17.8–19.5]	0.24	0.810
1990–1999	16.8 [16.1–17.5]	17.8 [17.0–18.5]	0.81	0.421
2000–2011	12.4 [11.8–13.0]	13.5 [12.9–14.1]	1.22	0.228
Women				
1980–1989	8.5 [8.00–8.90]	**6.9** [6.50–7.30]	2.41	**0.019**
1990–1999	6.0 [5.60–6.30]	5.6 [5.20–6.00]	0.92	0.360
2000–2011	4.4 [4.10–4.70]	4.1 [3.80–4.40]	1.05	0.298

Regional populations (2011) in the 36 regions with lowest lithium concentrations (3.02 million population) vs. 36 with highest concentrations (3.09 million population), representing the lowest vs. highest quartiles of lithium concentration in local water supplies. Boldface indicates significantly lower suicide rate with higher lithium concentrations, based on weighted *t*-scores.

correlation, again only for 1980–1989 (Table II). We also considered the data categorically, comparing suicide rates for the highest (6.56–60.8 μg/L) versus lowest (0.11–1.02 μg/L) quartiles of lithium concentrations in samples of similar size (each quartile with 36/145 sites, representing 3.09 and 3.02 million inhabitants, respectively; Table III). Again, there was no significant difference in corresponding suicide rates overall, but there was a significant association among women and during the 1980s (Table III).

The significant association of higher lithium concentrations with lower local suicide rates mainly in the 1980s and among women, if not merely a chance finding, is not readily explained. One speculative possibility might be a secular shift from major reliance on local supplies of drinking water to increased use of bottled mineral waters, which are popular in Italy. Most contain far higher concentrations of lithium than are found in typical natural water samples, in concentrations averaging 30 μg/L [CI: 10–50 μg/L] (4.3 [1.4–7.2] μEq/L), or 5.7-times higher than the average in natural water supplies (5.3 [4.1–6.5] μg/L] (Dinelli et al. 2010, 2012b). Indeed, there is evidence that the consumption of bottled mineral water has been rising in Italy over the past several decades (Zanasi and Parola 2013). The production of mineral water in Italy rose by approximately 264% between 1980 and 1990, and another 203% from 1990 to 2011, with a greater overall increase in annual consumption by women than men, of 741% between 1980 and 2011, based on research by the Beverfood Corporation (2007). It might be that a shift toward greater reliance on bottled mineral water than on tapwater, especially by Italian women, may have distorted or surmounted any effects of the trace concentrations of lithium in tapwater in recent decades.

If this hypothesis is valid, two considerations follow: (a) suicide rates in women should have been declining steadily from 1980 to 2011; (b) if an effect of bottled water can overcome natural effects of lithium in tapwater within a few years, that may have implications for mechanisms by which even trace concentrations of lithium may reduce suicide risk. The present findings, indeed, do indicate overall decreases of reported suicide rates from 1980 to 2011 in both women and men in the regions studied, whereas it is very likely that trace concentrations of lithium in specific regions have remained stable over time. Perhaps other trace minerals in tapwater may have adverse effects that may include increased suicide risk, which might be reduced by a shift to greater reliance on bottled water lacking such chemicals.

Regarding possible mechanisms of benefit, it seems very unlikely that the trace concentrations of lithium in typical samples of tapwater exert clinical effects on mood or behaviour comparable to the effects of clinically employed doses and associated circulating concentrations of lithium. Perhaps exposure to even low concentrations over years can exert cumulative effects. It is also notable, but unclear why, that lithium levels in tapwater were inversely correlated with suicide risk selectively among women in the present study as well as in two previous reports (Blüml et al. 2013; Sugawara et al. 2013). Similarly curious and inexplicable are associations of suicide rates with mountainous locations, with southern Italy, and with urban environments (Kim et al. 2011; Helbich et al. 2012, 2013).

In conclusion, an association between trace concentrations of lithium in drinking water and suicide rates remains uncertain, and the present findings yield only limited support for the proposal. Moreover, the basis of such an effect, if it occurs, is unclear, including its relationship to the apparent ability of long-term treatment with lithium carbonate in clinical doses to reduce rates of suicides and potentially lethal attempts in mood-disorder patients.

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Statement of Interest

The first two authors contributed equally to this paper. Dr Vichi provided statistical analyses; all authors contributed to data-interpretation and preparation of this report. No author nor immediate family member has financial relationships with commercial organizations that might appear to represent potential conflicts of interest for material presented.

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Supplemental data available online

Supplementary Tables 1–3 to be found online at http://informahealthcare.com/doi/abs/10.3109/15622975.2015.1062551.