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Research report

Trace lithium is inversely associated with male suicide after adjustment of climatic factors

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ABSTRACT

Background: Previously, we showed the inverse association between lithium in drinking water and male suicide in Kyushu Island. The narrow variation in meteorological factors of Kyushu Island and a considerable amount of evidence regarding the role of the factors on suicide provoked the necessities of adjusting the association by the wide variation in sunshine, temperature, rain fall, and snow fall.
Methods: To keep the wide variation in meteorological factors, we combined the data of Kyushu (the southernmost city is Itoman, 26°) and Hokkaido (the northernmost city is Wakkanai, 45°). Multiple regression analyses were used to predict suicide SMRs (total, male and female) by lithium levels in drinking water and meteorological factors.
Results: After adjustment of meteorological factors, lithium levels were significantly and inversely associated with male suicide SMRs, but not with total or female suicide SMRs, across the 153 cities of Hokkaido and Kyushu Islands. Moreover, annual total sunshine and annual mean temperature were significantly and inversely associated with male suicide SMRs whereas annual total rainfall was significantly and directly associated with male suicide SMRs.
Limitations: The limitations of the present study include the lack of data relevant to lithium levels in food and the proportion of the population who drank tap water and their consumption habits.
Conclusions: The present findings suggest that trace lithium is inversely associated with male but not female suicide after adjustment of meteorological factors.

1. Introduction

Several meta-analyses (Cipriani et al., 2005; Baldessarini et al., 2006; Cipriani et al., 2013) and randomized trials (Lauterbach et al., 2008; Oquendo et al., 2011) have shown anti-suicidal effects of lithium in people with mood disorders. Despite the fact that lithium levels in tap water are much lower than the so-called therapeutic levels, accumulating epidemiological studies investigate whether lithium may be effective for suicide attempt. An inverse association between lithium levels in drinking water and suicide rates was first reported in the USA from a sample of 27 Texas counties in 1990 (Schrauzer and Shrestha, 1990). Thereafter, we showed an inverse association between lithium levels in drinking water and suicide rates for 18 municipalities of Oita prefecture in Japan in 2009 (Ohgami et al., 2009). However, this association was not found in a sample derived from 47 subdivisions in the East of England (Kabacs et al., 2011) and the association remains uncertain in a sample derived from 145 sites in Italy where lithium concentrations and local suicide rates were not significantly inversely related, except in 1980–1989, particularly among women, and also, based on weighted least-squared, bivariate regression modeling, lithium concentrations were significantly and negatively associated with overall suicide rates (in women and men), but only in 1980–1989 (Pompili et al., 2015). A nationwide Austrian study found an inverse association between lithium levels in drinking water and suicide rates after adjustment of population density, per capita income, proportion of Roman

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Catholics, as well as the availability of mental health service providers (Kapusta et al., 2011). Furthermore, two recent studies, one conducted in Aomori prefecture of Japan (Sugawara et al., 2013) and the other in 34 province of Greece (Giotakos et al., 2013) also reconfirmed the inverse association between lithium levels in drinking water and suicide rates.

Moreover, in our most recent study (Ishii et al., 2015) investigating 274 municipalities of Kyushu Island in Japan, the associations of lithium levels in drinking water with suicide rates (total, male and female) were investigated adjusting for multiple variables such as proportion of elderly people, proportion of one-person households, proportion of people with college education or more, proportion of engaging in primary industry, overall unemployment rate, annual marriage rate, annual mean temperature and annual postal savings per person. As a result, lithium levels in drinking water were significantly and inversely associated with male suicide rates but not total or female suicide rates, suggesting that lithium in drinking water may be associated with the low risk of male suicide in the general population (Ishii et al., 2015).

Although we focused on Kyushu Island in the above study (Ishii et al., 2015), Japan has four large islands—Hokkaido, Honshu, Shikoku, and Kyushu. The northernmost island is Hokkaido whereas the southernmost island is Kyushu. The difference in latitude between Kyushu (the southernmost city is Itoman, 26°) and Hokkaido (the northernmost city is Wakkanai, 45°) is very large, suggesting considerable variations in climate (i.e. meteorological factors). There is a considerable amount of research concerning the role of meteorological factors on suicide such as the association of sunshine with suicide (Terao et al., 2002; Vyssoki et al., 2014), that of rainfall with suicide (Tsai, 2010; Tsai and Cho, 2012; Nicholls et al., 2006; Preti, 1998; Wu et al., 2014), and that of temperature with suicide (Tsai, 2010; Preti, 1998; Wu et al., 2014), thereby provoking the necessities of adjusting the association between lithium in drinking water and suicide ratios by meteorological factors.

In the present study, we investigated the association between lithium in drinking water and suicide rates of all 35 cities of Hokkaido Island and all 118 cities of Kyushu Island to adjust the association by the wide variation in sunshine, temperature, rain fall, and snow fall.

2. Methods

2.1. Suicide data

Taking the large differences in gender and age distribution of individual city populations into account, the standardized mortality ratio (SMR) of suicide in 2010 and 2011 was calculated for each individual city. We examined the data from Ministry of Health Labor and Welfare on suicide, and from Statistics Bureau, Ministry of Internal Affairs and Communications, and calculated total, male and female suicide SMRs for 2010 and 2011 across all 35 cities of Hokkaido Island and all 118 cities of Kyushu Island. We focused on the cities but not on the towns or villages in order to decrease heterogeneity of economic and cultural background as much as possible.

2.2. Measurement of lithium levels in drinking water

From 2010 to 2015, tap water samples (chiefly from the main rail station and/or the city office) of each city were taken and their lithium levels were measured by using mass spectroscopy analyzed by a third party. This method can measure very small amounts of lithium; the minimal amount of lithium that can be measured is 0.1 ppb (0.1 μg/l). If lithium levels of drinking water were measured at multiple points in the same city, the mean value was calculated. Although lithium levels were measured once in this study, we previously confirmed only a very small fluctuation in levels over time because the correlation coefficient between the lithium levels and those re-measured after 1 year in the same places was 0.998 (Ohgami et al., 2009). The distribution of lithium levels was also considerably skewed (skewness=4.3; kurtosis=24.0). We thus employed log-transformation (skewness=−0.01; kurtosis=0.26) in order to use parametric statistical procedures.

2.3. Meteorological factors

We initiated a crude model analysis of the association of lithium levels in drinking water and suicide SMRs (the average of suicide SMRs in 2010 and 2011 in total, male and female population) without any adjustment of the confounding factors (crude model). Furthermore, as previously mentioned, the associations were further investigated adjusting for meteorological factors such as annual total sunshine, annual mean temperature, annual total rainfall and annual total snowfall. Data from the Japan Meteorological Agency relating to these factors was available for two thirds of the 153 cities and was assumed to also represent the neighboring cities. Where meteorological data was unavailable for an individual city, the data from the neighboring city was extrapolated.

2.4. Statistical analysis

Due to differences in population size across the 153 cities, weighted least squares regression analysis adjusted for the size of each population was used to investigate the association of lithium levels in drinking water with the suicide SMRs as before (Ohgami et al., 2009; Ishii et al., 2015).

Multiple regression analyses were used to predict the average of suicide SMRs (total, male and female) in 2010 and 2011 by lithium levels in drinking water and meteorological factors (the average of annual total sunshine, annual mean temperature, annual total rainfall and annual total snowfall in 2010 and 2011). Multicollinearity was suspected if VIF value was above 10.

This study was approved by the ethics committee of Oita University Faculty of Medicine.

3. Results

3.1. Suicide rate, suicide SMR and lithium Levels

As for the average of suicide rate (2010 and 2011), 4039 deaths of 16981717.5 total population (23.8 per 100,000 population), 2871 deaths of 8040233.5 male population (35.7 per 100,000 population) and 1168 deaths of 8947561 female population (13.1 per 100,000 population) were identified in Kyushu and Hokkaido Islands. The average of mean total, male, and female suicide SMR (2010 and 2011) was 111.2 (SD 31.6; range 26.9–268.8), 119.1 (SD 38.6; range 0–245.0), and 97.1 (SD 44.9; range 0–319.0), respectively.

The mean lithium level in drinking water was 3.8 μg/l (SD 5.3; range 0.1–43) and the mean log-transformed lithium level in drinking water was 0.35 (SD 0.45; range −1 to 1.63). Annual mean

Table 1
Multiple regression analysis of total, male, female suicide SMRs.

Total	Model 1 (crude model)		Model 2 (adjusted model)	
Variables	β	p	β	p
Log-transformed lithium levels	−0.153	0.059	−0.129	0.070
Annual mean temperature			−0.545	0.000
Annual total sunshine			−0.121	0.174
Annual total rainfall			0.722	0.000
Annual total snowfall			−0.164	0.296
	$F=3.62$, $p=0.059$, Adjusted $R^2=0.017$		$F=14.9$, $p=0.000$, Adjusted $R^2=0.313$	
Male	Model 1 (crude model)		Model 2 (adjusted model)	
Variables	β	p	β	p
Log-transformed lithium levels	−0.225	0.005	−0.164	0.037
Annual mean temperature			−0.365	0.025
Annual total sunshine			−0.306	0.002
Annual total rainfall			0.401	0.000
Annual total snowfall			−0.289	0.094
	$F=8.07$, $p=0.005$, Adjusted $R^2=0.044$		$F=6.87$, $p=0.000$, Adjusted $R^2=0.162$	
Female	Model 1 (crude model)		Model 2 (adjusted model)	
Variables	β	p	β	p
Log-transformed lithium levels	0.012	0.883	0.014	0.870
Annual mean temperature			−0.275	0.125
Annual total sunshine			−0.089	0.412
Annual total rainfall			−0.022	0.859
Annual total snowfall			−0.223	0.242
	$F=0.022$, $p=0.883$, Adjusted $R^2=-0.006$		$F=0.844$, $p=0.520$, Adjusted $R^2=-0.005$	

temperature was 14.9 °C (SD 4.4; 6.3–24.4), annual total sunshine was 1735 h (SD 168; 1231–2049), annual total rainfall was 2023 mm (SD 604; 793–3578), and annual total snowfall was 123 mm (SD 237; 0–827).

3.2. The association between suicide SMRs and log-transformed lithium levels

As shown in Table 1, in the crude model, male suicide SMRs, but not total or female SMRs, were significantly and inversely associated with log-transformed lithium levels in drinking water. Fig. 1 shows the crude association between log-transformed lithium levels and male suicide SMRs. When the associations were further investigated adjusting for meteorological factors, male suicide SMRs, but not total or female suicide SMRs, were still significantly and inversely associated with log-transformed lithium levels in drinking water (Table 1).

3.3. The association between suicide SMRs and meteorological factors

Total suicide SMRs were significantly and inversely associated with annual mean temperature and significantly and directly associated with annual total rainfall (Table 1). Also as shown in Table 1, male suicide SMRs were significantly and inversely associated with annual total sunshine and annual mean temperature, and significantly and directly associated with annual total rainfall. Figs. 2 and 3 shows the crude association between annual total sunshine and male suicide SMRs and that between annual total rainfall and male suicide SMRs, respectively. Female suicide SMRs were not associated with any meteorological factors (Table 1). There was no multicollinearity.

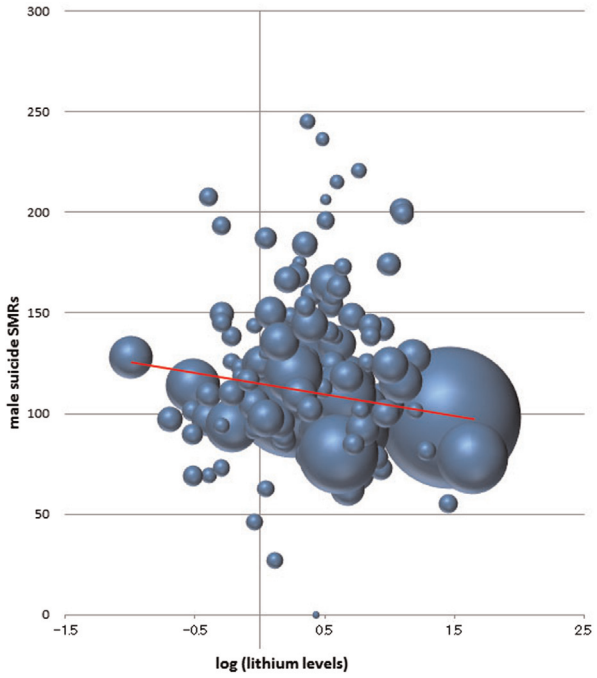

Fig. 1. Log-transformed lithium levels and male suicide SMRs. Male suicide SMRs = −10.5 × log-transformed lithium + 115. The size of sphere represents the size of populations.

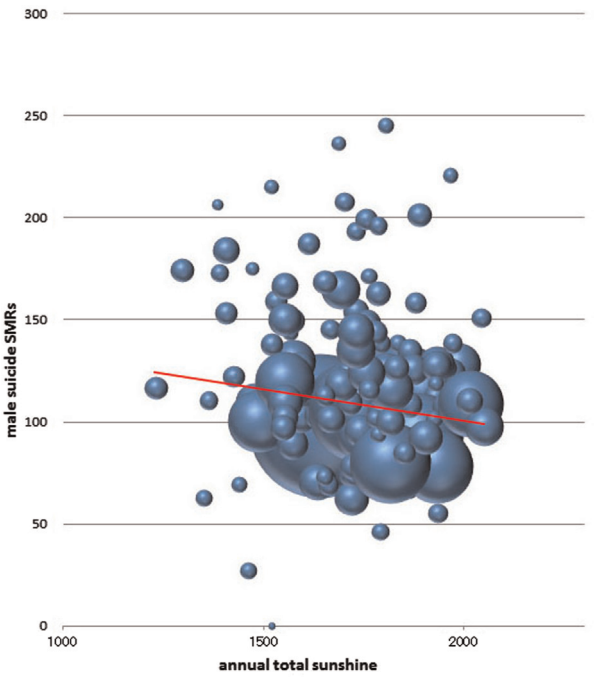

Fig. 2. Annual total sunshine and male suicide SMRs. Male suicide SMRs = −0.030 × annual total sunshine + 161. The size of sphere represents the size of populations.

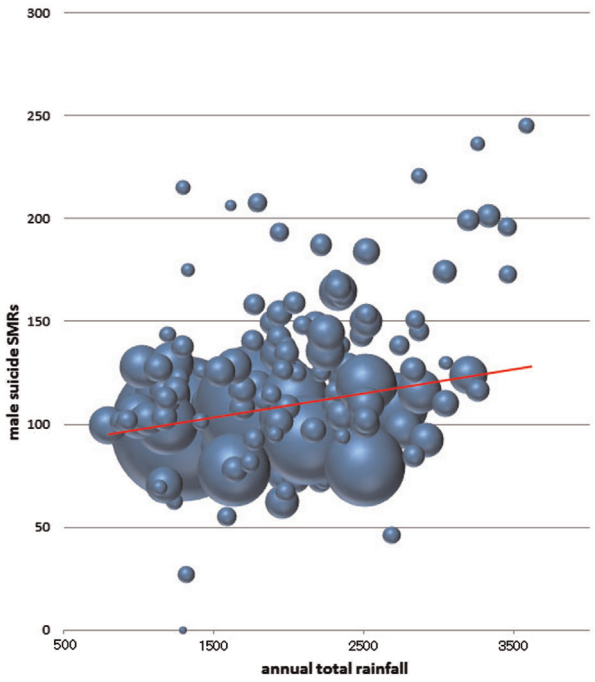

Fig. 3. Annual total rainfall and male suicide SMRs. Male suicide SMRs = 0.012 × annual total rainfall + 86. The size of sphere represents the size of populations.

4. Discussion

In the present study, after adjustment of meteorological factors, lithium levels were significantly and inversely associated with male suicide SMRs across 153 cities of Hokkaido and Kyushu Islands, which is in agreement with the findings of our previous study (Ishii et al., 2015). It should be noted that the present study applied a wide range of 4 meteorological factors to adjust the association between lithium in drinking water and suicide rate. Other differences were: our previous study investigated all 274 municipalities of Kyushu Island and socioeconomic factors were included as independent factors (Ishii et al., 2015) whereas this study focused on only cities. Furthermore, this study included Hokkaido Island in addition to Kyushu Island without adjusting for socioeconomic factors but with that of 4 meteorological factors. Moreover, our previous study used the data of 2011, but the present study used the average of the data of 2010 and 2011. Despite these differences, the inverse association between lithium and male suicide SMR was reconfirmed, demonstrating the robustness of the inverse association between lithium in drinking water and male suicide rate.

With regard to the gender difference, impulsivity and aggression have been associated with death by suicide (Gvion and Apter, 2011; Oquendo and Mann, 2000) and it has been observed that lithium administration decreases impulsive aggressive behavior in men (Sheard et al., 1976). Possibly, higher levels of lithium in the drinking water decrease suicide rates among men by reducing impulsivity and aggression (Sher, 2015). Another possible hypothesis is related to a potential role of testosterone in suicidal behavior because higher testosterone levels were associated with higher suicidality (Sher et al., 2012, 2014) and testosterone levels are much higher in men than in women (Shahidi, 2001). The administration of lithium has been reported to reduce testosterone levels (Thakur et al., 2003; Ghosh et al., 1991) and it is interesting to speculate that lithium reduces suicidality in men by decreasing testosterone levels (Sher, 2015).

With regard to the inverse association between annual total sunshine and male suicide SMRs, this is in partial agreement with our previous findings (Terao et al., 2002) of 47 prefectures of Japan in which multiple regression was performed to assess annual total sunshine, annual mean temperature, latitude, and annual mean individual income as independent variables in relation to suicide rate. The results of this study showed that annual total sunshine was the only individual variable to predict significant variance in suicide rate (Terao et al., 2002). Very recently, Vyssoki et al. (2014) showed that after accounting for the effects of season, a positive correlation was found between number of suicides and hours of daily sunshine remained for the day of suicide and up to 10 days prior to suicide, whereas a negative correlation was found between the number of suicides and daily hours of sunshine for the 14–60 days prior to the suicide event. A significant gender effect was also present as, for females, the most highly significant correlations were the positive ones for up to 10 days prior to the suicide event, whilst for males the most highly significant correlations were the negative ones for the 14 days to 60 days prior to the suicide (Vyssoki et al., 2014). Although the effects of sunshine seem complicated, the negative correlations for the 14–60 days particularly in males are in agreement of the present findings.

Unexpectedly, the present findings showed a significant direct association between rainfall and suicide in male and total population. Tsai (2010) has also reported a significant direct association between rainfall and suicide in total and in the female population, with a trend in male population in Taiwan. However, subsequently Tsai and Cho (2012) showed a significant inverse association between rainfall and suicide in a different analysis. Other researchers have also reported the inverse associations between rainfall and suicide (Nicholls et al., 2006; Preti, 1998; Wu et al., 2014). It is unknown why our findings do not conform with the literature showing an inverse association. In our study, snowfall was not associated with suicide in total, male, or female population. We also investigated the association between the summation of rainfall and snowfall and suicide with the result that the association still remained to be direct and statistically significant (data not shown). Further studies are required to investigate the association between the amount of rainfall and lithium levels in drinking water longitudinally.

Both total and male suicide SMRs were significantly and inversely associated with annual mean temperature. This is in partially accordance with some reports (Tsai, 2010; Preti, 1998; Wu et al., 2014) but not with other reports (Tsai and Cho, 2012). Probably, methodological differences such as regions, observation years, other adjustment factors and so on might have brought about this discrepancy. Nonetheless, the present findings suggest that higher temperature may facilitate male suicide prevention with adjustment of trace lithium, sunshine, rainfall, and snowfall.

The limitations of the present study include the lack of data relevant to lithium levels in food and the proportion of the population who drank tap water and their consumption habits. Moreover, it is unknown how many people shifted within and out of municipalities and how long they drank tap water whilst they were within each municipality. Moreover, although we previously confirmed only a very small fluctuation in levels over time, there are a number of variables that may influence lithium levels during the course of time and it cannot be denied that lithium levels may fluctuate over time. Finally, this type of study has the possibility of ecological fallacy and we should consider the results cautiously. To resolve these limitations, we are now performing a comparison study of serum lithium levels of suicide attempters and control group.

In conclusion, the present findings suggest that trace lithium is inversely associated with male but not female suicide after adjustment of meteorological factors.

Contributors

Ippei Shiotsuki: Study design, Data collection, Data analyses, Paper writing.

Takeshi Terao: Study design, Data collection, Data analyses, Paper writing.

Nobuyoshi Ishii: Data collection, Submission of application to the local ethics committee.

Shohei Takeuchi: Data collection, Supervised and oversaw the project from an epidemiological perspective.

Yoshiki Kuroda: Data collection, Supervised and oversaw the project from an epidemiological perspective.

Kentaro Kohno: Data collection, management of project.

Yoshinori Mizokami: Data collection, management of project.

Koji Hatano: Data collection, management of project.

Sanshi Tanabe: Data collection, management of project.

Masayuki Kanehisa: Data collection, management of project.

Noboru Iwata: Data analyses, Supervised and oversaw the project from an epidemiological perspective.

Shinya Matusda: Data analyses, Supervised and oversaw the project from an epidemiological perspective.

All authors contributed to and approved the submitted manuscript.

Role of funding source

The sources of funding were not involved in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

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