Trace lithium in Texas tap water is negatively associated with all-cause mortality and premature death

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Abstract (75 word limit)

Lithium in tap water was previously found to have life-extending effects across 18 Japanese municipalities. Using a larger dataset with several Texas counties, our study shows that lithium concentrations in tap water are negatively associated with all-cause mortality (r = -0.18, p = 0.006, 232 counties) and years of potential life lost (r = -0.22, p = 0.001, 214 counties). Thus, our present findings extend and reinforce lithium's purported life-prolonging effect in humans.

Keywords: lifespan, longevity, GSK3, lithium, healthspan

Introduction

Lithium is an essential trace element that is most commonly known for its use in treating bipolar disorder; albeit at relatively high doses (900-1200 mg/day) where adverse events including renal damage, thyroid disorders, and gastrointestinal disturbances have been observed (Malhi and Tanouis 2011). At much lower doses, lithium acts as a nutrient exerting positive effects not only on mental health but also cognitive function and inflammatory status (Marshall 2015). Furthermore, several studies have documented a life-prolonging effect of low-dose lithium in *Caenorhabditis elegans,* yeast, and drosophila (McColl et al. 2008; Zarse et al. 2011; Tam et al. 2014; Castillo-Quan et al. 2016). In humans, environmental exposure to trace amounts of lithium via drinking water was inversely associated with all-cause mortality in 18 neighboring Japanese municipalities (Zarse et al. 2011).

Indeed, the effects of trace lithium on lifespan are impressive since the concentrations of lithium in water can be 1000-fold less then the therapeutic doses used for bipolar disorder. However, to our knowledge, the findings from Zarse and colleagues (Zarse et al. 2011) represent the only study examining the life-prolonging effects of trace lithium in humans. To increase the generalizability of their findings, it is imperative that the negative link between trace lithium in drinking water and all-cause mortality be examined amongst other populations. Here, we examined the association between trace lithium and all cause-mortality with a much larger dataset using data readily obtained from 234 U.S. Texas counties. We also examined the association between trace lithium and premature death as indicated by years of potential life lost.

Methods

Data acquisition

A total of 6,180 water samples from public wells since 2007 were obtained from the Texas Water Development Board Groundwater Database, assessed, and then averaged for 234 of 254 Texas counties. Mean lithium levels in the Texas counties ranged between 0.003 and 0.539 mg/L.

Age-adjusted all-cause mortality rates as well as suicide mortality rates (code X60-X84, intentional self-harm) from 2006-2015 were obtained from the Center for Disease Control Wonder's compressed mortality database. In total, data for all-cause mortality were obtained from 253 counties as one county had their mortality rate suppressed. Due to confidentiality constraints, sub-national death counts and rates are suppressed when the number of deaths is less than 10. For suicide mortality, we obtained data for 140 counties, as the remaining counties had their suicide mortality rates either suppressed or flagged as unreliable. As per the CDC Wonder Database, a death rate based on fewer than 20 deaths has a relative standard error of 23% or more, and is therefore considered statistically unreliable.

Rates of premature death, from 2011-2016 were obtained from the National Center for Health Statistics – Mortality Files, and represent the years of potential life lost before the age of 75. Every death occurring before the age of 75 contributes to the total number of years of potential life lost. In total, we were able to obtain data on years of potential life lost from 214 counties as data for remaining 40 counties were missing. Both age-adjusted all-cause mortality and years of potential life lost are presented as a rate per 100,000 and are age-adjusted to the 2000 US population.

We also obtained data pertaining to socioeconomic status for all 234 counties with lithium concentration data from 2011-2016 including median household income, the percent of unemployment, and the percentage of adults with college education. The median household income (US Census Bureau's Small Area Income and Poverty Estimates program) is the income at which half the households earn more and half the households earn less and is a well-recognized indicator of income and poverty. The percent of unemployment (Bureau of Labor Statistics) represents the percentage of the population ages 16 and older unemployed but seeking work. The percentage of adults having some post-secondary education (American Community Survey) represents the percentage of adults aged 25-44 with post-secondary education, such as enrolment in vocational/technical schools, junior colleges, or four-year colleges. It includes individuals who pursued education following high school but did not receive a degree.

Statistics

Lithium concentrations were log-transformed prior to correlational analysis as previously described (Ohgami et al. 2009; Zarse et al. 2011; Bluml et al. 2013). Kolmogorov-Smirnov tests for normality indicated that log lithium and years of potential life lost were normally distributed, whereas rates of age-adjusted all cause mortality was not. Thus, the relationship between lithium concentrations and age-adjusted all cause mortality was assessed using a Spearman's correlation, whereas the relationship between lithium concentrations and years of potential life lost was performed using a Pearson's correlation. Partial correlations were performed to assess the relationship between

lithium concentrations and all-cause mortality and years of potential life lost while adjusting for suicide mortality and socioeconomic status. All statistical tests were performed using SPSS (IBM Corporation, NY, US) and statistical significance was set to $p \leq 0.05$.

Results

Our results show that trace lithium concentrations are negatively associated with all-cause mortality across several Texas counties (Figure 1a). A similar negative association was detected between trace lithium concentrations and years of potential life lost (Figure 1b). Similar to the study by Zarse and colleagues (Zarse et al. 2011), we also adjusted for suicide mortality rates as trace lithium in drinking water has been negatively linked with suicide mortality across the Texas counties (Bluml et al. 2013). Our findings indicate that after adjustment for suicide mortality the negative association between trace lithium concentrations and all-cause mortality was no longer significant, whereas the negative association between trace lithium concentrations and years of potential life lost remained significant (Table 1). In addition to suicide mortality, we also controlled for factors related to socioeconomic status including: education level, median household income, and unemployment status. Our findings indicate that for all-cause mortality and years of potential life lost, their negative associations with log lithium concentration remained significant when controlling for these factors individually and when combined together (Table 2).

Discussion

In this study, we show that trace levels of lithium in the Texas drinking water, which are well below the concentrations used for bipolar disorder, is negatively associated with all-cause mortality and years of potential life lost. These findings build upon those from a previous study that initially discovered a similar negative association between trace lithium in water and all-cause mortality in Japan (Zarse et al. 2011). As with the study performed by Zarse et al. (Zarse et al. 2011), our study is observational and ecological in its design, and therefore a causal link between lithium exposure and reduced mortality may not be established. Although life-long intervention studies in humans may not be feasible, our study enhances the generalizability of the findings from Zarse and colleagues (Zarse et al. 2011), and reinforces the notion that lithium may extend lifespan in humans.

Lithium's life-prolonging effects has been well established in other organisms such as *C. elegans,* yeast, and drosophila; and several experiments have been performed to better understand the underlying cellular mechanisms explaining this effect (McColl et al. 2008; Zarse et al. 2011; Tam et al. 2014; Castillo-Quan et al. 2016). In both drosophila and *C. elegans,* lithium supplementation was shown to have partially overlapping effects with dietary restriction, which is a well-established anti-aging intervention that extends lifespan (de Cabo et al. 2014). In addition, lithium is a well-known inhibitor of glycogen synthase kinase 3 (GSK3), and GSK3 inhibition has been shown to be required for lithium's life-prolonging effects in *C. elegans* and drosophila models (McColl et al. 2008; Castillo-Quan et al. 2016). In a recent study by Castillo-Quan et al. (2016), lithium supplementation was found to prolong life in drosophila by

reducing cellular stress through GSK3 inhibition. In addition to GSK3, experiments with *C. elegans* show that low dose lithium treatment also alters histone methylation, chromatin remodeling, and mitochondrial turnover, which can all influence longevity (McColl et al. 2008; Tam et al. 2014; Madeo et al. 2015). Nonetheless, whether these cellular mechanisms can explain lithium's apparent life-prolonging effects in humans remains unclear and future studies are required.

Lithium is commonly used for the treatment of bipolar disorder and several ecological studies, including one in Texas (Bluml et al. 2013), have shown a negative link between trace lithium in drinking water and suicide mortality. After adjusting for suicide mortality the negative association between trace lithium and all-cause mortality was no longer significant, whereas the negative association between trace lithium and years of potential life lost was not affected. It should be noted that in both cases the sample size was drastically reduced, as we were only able to obtain reliable suicide mortality rates for 140 Texas counties. In turn, the number of counties with lithium concentration, all-cause mortality/years of potential life lost, and suicide mortality together was only 135. In addition, as years of potential life lost emphasize premature death, it may be a better indicator of the effects of lithium on lifespan. In this case, our data suggests that Texas counties with greater lithium concentrations in their drinking water display lower rates of premature death even after adjusting for suicide mortality.

Along with controlling for suicide mortality, we also controlled for socioeconomic status, since low socioeconomic status has been negatively linked with life expectancy (Stringhini et al. 2017). Specifically, we tested the correlations between log lithium concentrations and all-cause mortality and premature death, while controlling

for education, median income, and unemployment status. Interestingly, for all-cause mortality and premature death, the negative associations with log lithium concentrations remained statistically significant despite controlling for these factors individually and when combined together. Thus, these results suggest that the associations between trace lithium in water and human lifespan in Texas are less likely confounded by socioeconomic status.

The average American adult consumes 1.1 L of water as a beverage per day with 0.644 L from tap water, and both the average tap water and total water consumption are significantly reduced in older populations (Drewnowski et al. 2013). According to our study and the study done by Zarse and colleagues (Zarse et al. 2011), this could have important implications given the putative life-prolonging effects of trace lithium in drinking water. Indeed, this could also have implications for geriatric mental health, as older adults are at increased risk for depression for several factors including disease development, living alone, and functional disability (Sozeri-Varma 2012; Lutz and Fiske 2017).

In summary, our study compliments and extends the findings from Zarse et al., (Zarse et al. 2011) who first demonstrated a negative association between trace lithium and all-cause mortality in a Japanese cohort. Future studies examining the link between lithium in drinking water and lifespan in other regions and populations will help in further determining whether lithium can promote longevity in humans.

Acknowledgements

Conflict of Interests

The authors declare none.

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Table 1. Partial correlations between log lithium levels and all-cause mortality and years of potential life lost while adjusting for suicide mortality (135 counties).

model	r	p-value
All-cause mortality	-0.11	0.19
Years of potential life lost	-0.22	0.01

Table 2. Partial correlations between log lithium levels and all-cause mortality and years of potential life lost while adjusting for socioeconomic status.

model	r	*p*-value
All-cause mortality		
education	-0.28	<0.0001
median household income	-0.25	<0.0001
unemployment status	-0.20	0.003
combined	-0.26	<0.0001
Years of potential life lost		
education	-0.18	0.005
median household income	-0.16	0.01
unemployment status	-0.14	0.03
combined	-0.17	0.009

For all cause mortality, 232 counties were analyzed; for years of potential life lost, 214 counties were analyzed. Education, represents the % of population ages 25-44 within a county that have some post-secondary education; median household income, is the income at which half the households earn more and half the households earn less; unemployment status is the percentage of the population ages 16 and older unemployed but seeking work.

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FIGURE LEGENDS

Figure 1. Trace Li^+ levels in drinking water is negatively associated with all-cause mortality (**a**) and years of potential life lost (**b**) across several Texas counties. All rates are per 100,000 of the population.
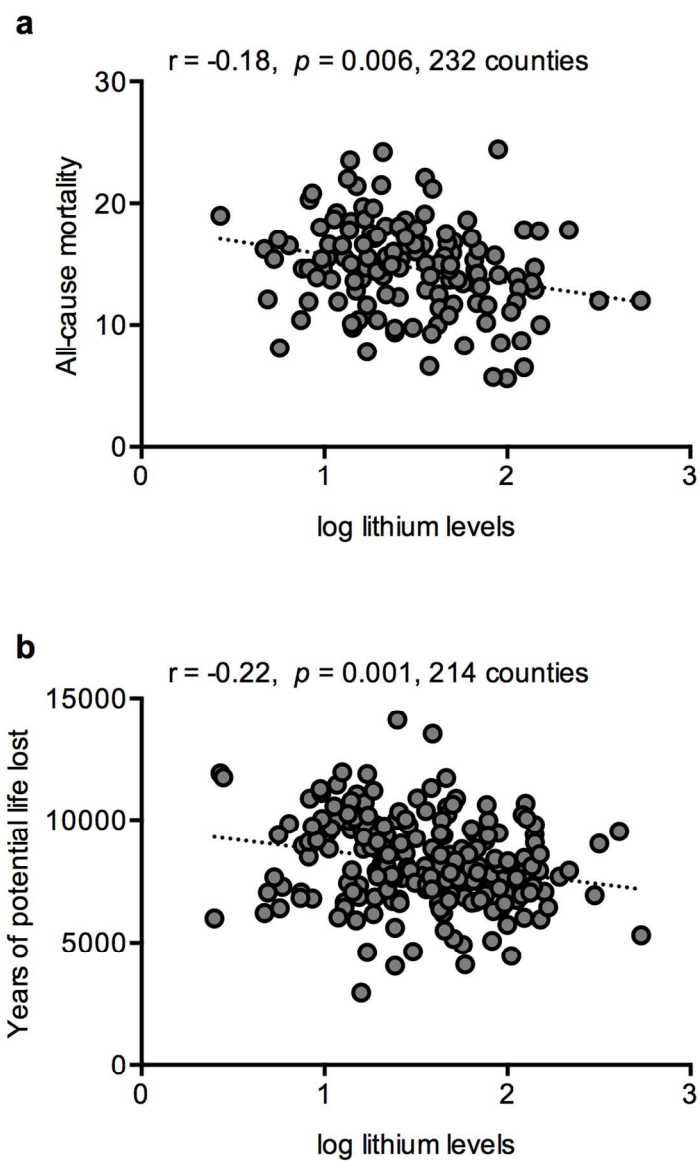
a

r = -0.18, *p* = 0.006, 232 counties

b

r = -0.22, *p* = 0.001, 214 counties

Figure 1. Trace Li+ levels in drinking water is negatively associated with all-cause mortality (a) and years of potential life lost (b) across several Texas counties. All rates are per 100,000 of the population.

103x153mm (300 x 300 DPI)