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Association between naturally occurring lithium in drinking water and suicide rates: A systematic review and meta-analysis of ecological studies

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Key words: Lithium in drinking water, suicide, ecological studies, epidemiology of suicide, suicide prevention, systematic review, meta-analysis.

ABSTRACT

Background

The prevalence of mental health conditions and national suicide rates are increasing in many countries. Lithium is widely and effectively used in pharmacological doses for the treatment and prevention of manic/depressive episodes, stabilising mood and reducing the risk of suicide. Since the 1990s, several ecological studies have tested the hypothesis that trace doses of naturally occurring lithium in drinking water may have a protective effect against suicide in the general population. We synthesised the global evidence on the association between lithium levels in drinking water and suicide mortality rates.

Method

The MEDLINE, EMBASE, Web of Science and PsycINFO databases were searched to identify eligible ecological studies published between 1st January 1946 and 10th September 2018. Standardized regression coefficients for total (i.e. both sexes combined), male and female suicide mortality rates were extracted and pooled using random effects meta-analysis. The study was registered with PROSPERO (number CRD42016041375).

Results

The literature search identified 415 articles; of these, 15 ecological studies were included in the synthesis. The random effects meta-analysis showed a consistent protective (or inverse) association between lithium levels/concentration in publically available drinking water and total (pooled β -0.27 [95%CI: -0.47, -0.08]; p=0.002, I^2=83.3%), male (pooled β -0.26 [95%CI: -0.56, 0.03]; p=0.08 I^2=91.9%), and female (pooled β -0.13 [95%CI: -0.24, -0.02]; p=0.03, I^2=28.5%) suicide mortality rates. Similar protective association was also observed in the six studies included in the narrative synthesis, and subgroup meta-analyses based on the higher/lower suicide mortality rates and lithium levels/concentration.

Conclusions

This synthesis of ecological studies, which are subject to the ecological fallacy/bias, supports the hypothesis that there is a protective (or inverse) association between lithium intakes from public drinking water and suicide mortality at the population level. Naturally occurring lithium in drinking water may have the potential to reduce the risk of suicide and may possibly help in mood stabilisation, particularly in populations with relatively high suicide rates and geographical areas with a greater range of lithium concentration in the drinking water. All the available evidence suggest that randomised community trials of lithium supplementation of the water supply might be a possible means of testing the hypothesis, particularly in communities (or settings) with demonstrated high prevalence of mental health conditions, violent criminal behaviour, chronic substance abuse and risk of suicide.

Introduction

Suicide is a leading cause of mortality worldwide, responsible for over 800,000 deaths per year, and is the second most common cause of death in people aged 15-29 years(1). In 2018, there were 6,507 suicides registered in the United Kingdom (UK), an age-standardised rate of 11.2 deaths per 100,000 population, with a male: female ratio of 3:1(2). This male predominance is observed in almost all countries(3). People with mental health conditions, especially those with mood disorders such as depression and bipolar (labelled manic-depressive illness until 1980) are at substantially increased risk of suicide(4). The prevalence of mental health conditions and national suicide rates are increasing in many countries. Findings from population-based surveys suggest that suicidal ideation, suicide planning and suicide attempts have especially increased over the past 10 years among young people (aged ≤25 years), and that these increases have co-occurred with increasing prevalence of mental health conditions (especially mood disorders such as depression and bipolar) and chronic substance abuse(5). Bipolar disorder affects about 1 in 100 people globally - without treatment, it can become a relentless cycle of emotional highs and lows.

Since the discovery of its therapeutic effect (and dose) by John Cade (an Australian psychiatrist) in 1949, lithium is widely and effectively used in pharmacological doses in psychiatry for the treatment and prevention of manic and depressive episodes, stabilising mood and reducing the risk of suicide in people with mood disorders(6, 7). Mood disorders are characterised by a 30-50 times increased risk of suicide that can be reduced with lithium treatment. Lithium also appears to have an anti-suicidal effect that might be independent from its mood stabilising property – there is some evidence that it decreases aggression and possibly impulsivity, which might be another mechanism mediating the anti-suicidal effect[5]. The recommended serum levels for lithium range between 0.6 and 1.0 mmol/l for maintenance therapy of bipolar disorder. However, the optimal blood level at which lithium exerts a possible preventive effect against suicide has not been confirmed and the mechanism of action by which this is achieved is complex and not fully characterised(8), in particular the potential effect of trace doses of lithium is not clear. In one small randomised controlled trial, micro-doses of lithium (400µg daily) taken by former drug users showed an improvement in mood when compared to placebo(9), suggesting that doses of lithium considerably lower than those generally used in psychiatry may have the potential to influence mood and possibly reduce suicide risk.

Lithium is a naturally occurring element and is found in variable amounts in vegetables, grains, spices and drinking water. It is present in trace amounts in virtually all rocks, and is mobilised by weathering into soils, ground and standing water, and thus into the public water supply in varying concentrations(10). Its health benefits and curative powers have been known for centuries (e.g. Lithia Springs, Georgia, USA). In certain areas, particularly those close to sources of briny water such as northern Argentina, concentrations of up to 1000 micrograms/L have been reported(11). In the first ecological study on the subject, Schrauzer &

Shrestha (1990) reported that the average incidence rates of suicide and violence (i.e. homicide and rape) in 27 counties of Texas, USA, over a 10-year period, were consistently lower in counties with relatively high natural lithium levels in the drinking water compared with those with medium or low levels. Based on these findings, the authors hypothesized that lithium may exert a moderating effect on suicidal and violent criminal behaviour at levels that may be found in public water supplies. Since the publication of this report in 1990, a number of ecological studies from the US, Japan, and Europe have tested the hypothesis that trace doses of naturally occurring lithium in drinking water may have a protective effect against suicide in the general population.

Natural lithium is a mixture of two stable isotopes, lithium-6 and lithium-7. Lithium-7 accounts for over 92% of the natural abundance of the element. The health benefits and curative powers of naturally occurring lithium in water are known for centuries. For example, the Lithia Springs (in Georgia, USA), an ancient Native American sacred medicinal spring, with its natural lithium-enriched water, is reputed for its health-giving properties and is the source of the brand called ‘Lithia Spring Water’. Lithium drinks were so much in demand in the early 20th century that when the 7-Up commercial drink was created in 1929, it contained the element and was called ‘Bib-Label Lithiated Lemon-Lime Soda’. The US Food and Drug Administration banned the use of lithium in soft drinks and beer in 1948 and 7-Up was reformulated. It has been suggested that the 7 in 7-Up referred to the atomic mass of lithium and the Up referred to ‘mood or lithium lift’.

The objective of this study was to determine the association between lithium levels/concentration in public drinking water and local/regional suicide rates in the general population. To our knowledge, this is the most comprehensive synthesis of the epidemiological evidence on the subject.

Method

We conducted a systematic review and meta-analysis of the association between naturally occurring lithium content in publically accessible sources of drinking water and local/regional suicide rates. This report is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(12). The study protocol was registered with PROSPERO (number CRD42016041375) https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=41375.

Search strategy and selection criteria

We searched four electronic databases (MEDLINE, EMBASE, Web of Science and PsycINFO), without any language restrictions, for articles published between 1 January 1946 and 10 September 2018. The search terms included: Lithium AND drinking water OR public water OR water OR tap water AND suicide OR mortality OR violent OR violence. The full search strategy used for Embase in Ovid is given in Figure S1 in the supplementary data. Articles were eligible for inclusion if they were based on original ecological, population-based studies (i.e. analysing aggregate group data defined by geopolitical boundaries rather than individuals) that evaluated the association between lithium levels/concentrations in publically accessible sources of drinking water and local/regional suicide mortality rates. Articles were excluded if the water samples for lithium measurement were obtained more than 10 years before or after the time period for which suicide rates were measured.

Titles and abstracts of the identified articles were screened by SF or IR for potentially relevant studies, and the full text was retrieved for articles identified at this screening stage. Two independent reviewers (either SF and AM, or IR and AM) carried out assessment of the full text articles for inclusion in the synthesis, and any disagreements were resolved by discussion. The references of all full text articles and relevant review articles were also searched for additional studies. Authors of ongoing studies, that fit the selection criteria, were also contacted to request unpublished data.

Data extraction and analysis

The relevant data from individual articles were extracted using a preconceived and standardized data extraction form. Information extracted included: first author's name, year of publication, country and region, size of the population studied, methodology of lithium sampling and laboratory analysis, average lithium levels/concentrations in drinking water, mean total suicide mortality rate and/or standardised mortality ratio (SMR), time period of the suicide data, list of covariates that were adjusted for in the analysis, and outcome measure (statistical methods and effect size and standard error). Corresponding authors were contacted for any data not presented in the published article. For two of the included studies(13, 14), standardized regression coefficients were not included in the published articles, but were calculated from data supplied by the authors. Where only the standardized regression coefficient and p value or t value were reported, the standard error of the standardized regression coefficient was estimated using the method of Altman and Bland(15) (standard errors calculated by this method were adjusted for one study(16) to account for the low sample size).

Quality assessment of included studies

To assess the quality of epidemiological ecological studies, we adapted the checklists produced by Tu & Ko(17) and Betran et al.(18) to give five evaluation criteria, which were used to assess each study (Table S1 in supplementary data). The evaluation criteria assessed whether the study subjects were representative of the conclusions being drawn, whether statistical methods were used appropriately, whether confounders were adjusted for appropriately, if key elements of the study design were presented and justified, and discussion of limitations such as the ecological fallacy. Quality assessments were performed by two independent reviewers (either SF and AM or IR and AM) and any discrepancies resolved by consensus. The results of the quality assessment were not used to decide on inclusion or exclusion of studies.

Data synthesis

Whilst acknowledging the concerns with pooling non-randomized study designs(19), where the comparisons were deemed reasonably homogenous the standardized regression coefficients and their corresponding standard errors were pooled using random effects meta-analyses. Heterogeneity was assessed with I^2 and Cochran's Q. Separate meta-analyses were conducted for total, male and female suicide rates. Where both adjusted and unadjusted regression coefficients were presented, the unadjusted regression coefficient was used in preference, when available. The exposure to lithium was determined according to the lithium levels/concentration in drinking water, or log-lithium level; and the outcome variable was either a standardized regression coefficient of SMR or suicide mortality rate. All analyses were carried out in R 3.5.0(20) using the metafor package(21). Subgroup analyses were conducted to assess heterogeneity according to whether the study took place in a country where the mean age-adjusted total suicide mortality rate in the WHO 2015 data(22) was either ≥10 per 100,000 (high suicide rate countries i.e. Japan, Austria, Lithuania and the USA), or <10 per 100,000 (low suicide rate countries i.e. Greece, Italy and the UK), and according to the highest observed lithium levels in the sampled drinking water (≥80μg/l or <80μg/l). Quality assessment was also used to explain heterogeneity between studies. In the primary meta-analyses (all eligible studies of total, male and female suicide rates), we also performed a sensitivity analysis to evaluate robustness and stability by sequentially omitting one study at a time.

Results

A flowchart describing the study selection process is given in Figure 1. The literature search identified 415 articles – after exclusion of duplicate titles and abstracts, 260 articles were screened and 41 were selected for full-text evaluation. Of these, 15 articles fulfilled the selection criteria and were included in the synthesis, four studies were conducted in Japan, four in Austria, three in USA, and one each in England, Greece, Italy and Lithuania.

In the included ecological studies, drinking water samples were collected from publically available tap water sources in a variety of locations or from public wells. Most water samples were analysed by mass spectrometry or inductively coupled plasma emission spectroscopy. Three studies used water supply company's data on water composition. Eleven studies controlled for one or more confounding variables in the analyses; and six studies controlled for a measure of socioeconomic status (e.g. proportion of population with a college degree, unemployment rate, average income). A variety of other possible confounders were adjusted for in different studies including measures of local climate, altitude and density of medical professionals. Suicide mortality data were obtained from government statistics in all the studies and covered time periods of between one year(23) and 11 years(24, 25). All studies included the overall suicide mortality rate across all age groups in the geographical areas covered, 14 studies presented data on total suicide rates, and 10 each presented data on male and female suicide rates. All but three studies(14, 24, 26) obtained lithium levels/concentration data over a range of years that overlapped with the population-based aggregate suicide mortality data. The number of drinking water samples taken ranged from 22(27) to 6460(28). The mean lithium levels in the drinking water samples ranged from 3·8 μg/l(29) to 46·3 μg/l(30). The total study populations ranged from 1,109,261(27) to 22,097,948(30) and the total suicide mortality rate per 100,000 per year ranged from 7.53(25) to 27(27).

Study quality

Of the nine studies included in the meta-analysis, three fulfilled all five of the evaluation criteria, four fulfilled four of the criteria, one fulfilled three, and one fulfilled two. Failure to adjust for covariates was the most common methodological omission. Studies fulfilling at least four of the criteria were considered to be of high quality. Details of the quality assessment are given in Table S1 in the supplementary data.

Meta-analysis of association between lithium levels in drinking water and suicide mortality rates

The studies included in the meta-analysis are summarized in Table 1. Eight studies that reported the association between lithium levels in drinking water and suicide mortality as a standardized regression coefficient of either SMR or suicide rates on log lithium levels, were eligible for inclusion in the meta-analysis. One further study(24) reported the standardized regression coefficient of age-standardized suicide mortality rate on untransformed lithium levels – the meta-analysis was repeated with and without the inclusion of this study. Four of the articles identified in the literature search(28, 31-33) were multiple analyses carried out on the same Austrian data – only the original study(28) was included in the meta-analysis. Three studies conducted in Japan had overlapping drinking water sample areas(23, 29, 34) – only the study with the largest sample size(29) was included in the meta-analysis. One study examined suicide rates over three ten-year periods(25) – only the results for the last period were included in the meta-analysis as this overlapped with the time when the drinking water samples were collected. Two of the included studies were conducted in Japan, two in the USA, and one each in England, Austria, Greece, Italy and Lithuania. A range of different population sizes and municipalities were evaluated, from entire countries to individual provinces and prefectures. Two studies(27, 29) excluded suicides that were not registered in cities, otherwise all suicides in the regions studied were included.

Total (i.e. both sexes combined) suicide mortality rate (Figure 2)

Eight eligible studies examined the association between lithium levels in drinking water and total suicide mortality rates – seven of these studies reported a protective (i.e. inverse or negative) association between lithium levels and total suicide rates, which was statistically significant in five of the seven studies. The random effects meta-analysis showed a statistically significant protective (or inverse) association between lithium levels and total suicide rates (pooled β -0.27 [95%CI: -0.47, -0.08]; p=0.002, I^2=83.3%). To assess the impact of relatively high heterogeneity between the studies, we conducted a sensitivity analysis. The heterogeneity was reduced most on excluding the study by Liaugaudaite *et al*.(27) and the meta-analysis yielded a pooled β of -0.17 [95%CI: -0.25, -0.09]; p<0.0001, I^2=<0.01%. The results of one study(24) were derived from a standardized regression of SMR on untransformed lithium values rather than log lithium – omitting this study had no effect on the results (pooled β -0.29 [95%CI: -0.52, -0.06]; p=0.01, I^2=85%). We obtained a similar result (β -0.25 [95%CI: -0.50, -0.01]; p=0.04, I^2=86.0%), when we repeated the meta-analysis including only the studies considered to be of high quality.

Male suicide mortality rate (Figure 3)

Seven eligible studies examined the association between lithium levels in drinking water and male suicide mortality rates – five of these studies reported a protective (or inverse) association between lithium levels and male suicide rates, which was statistically significant in three of the five studies. On the other hand, two studies reported non-significant positive association. The random effects meta-analysis showed an protective (or inverse), but statistically non-significant, association between lithium levels and male suicide rates (pooled β -0.26 [95%CI: -0.56, 0.03]; p=0.08 I^2=91.9%). In the sensitivity analyses, the heterogeneity was reduced most on excluding the study by Liaugaudaite *et al*.(27), and the meta-analysis yielded a pooled β of -0.12 [95%CI: 0.28, 0.03]; p=0.13, I^2=64.0%. We obtained a similar result (β -0.21 [95%CI: -0.53, 0.10]; p=0.19, I^2=93.0%), when we repeated the meta-analysis including only the studies considered to be of high quality.

Female suicide mortality rate (Figure 4)

Seven eligible studies examined the association between lithium levels in drinking water and female suicide mortality rates – five of these studies reported a protective (or inverse) association between lithium levels and female suicide rates, which was statistically significant in two of the five studies. On the other hand, two studies reported non-significant positive association. The random effects meta-analysis showed a statistically significant protective (or inverse) association between lithium levels and female suicide rates (pooled β -0.13 [95%CI: -0.24, -0.02]; p=0.03, I^2=28.5%). In the sensitivity analyses, the heterogeneity was reduced most on excluding the study by Shiotsuki *et al*.(29), and the meta-analysis yielded a pooled β of -0.17 [95%CI: -0.28, -0.07]; p=0.001, I^2=0.02%. We obtained a similar result (pooled β -0.11 [95%CI: -0.22, -0.001]; p=0.05, I^2=26.0%), when we repeated the meta-analysis including only the studies considered to be of high quality.

Meta-analysis by higher/lower total suicide mortality rates, according to the WHO data (Figure S2 supplementary data)

The random effects meta-analysis, including five studies from countries with higher suicide rates, showed a statistically significant protective (or inverse) association between lithium levels and total suicide rates (pooled β -0.40 [95%CI: -0.68, -0.12]; p=0.005, I^2=86.0%); whereas, including only the three studies from countries with lower suicide rates yielded a pooled β of -0.11 [95%CI: -0.23, 0.01]; p=0.08, I^2=0.0%, with no heterogeneity.

Meta-analysis by higher/lower observed lithium levels in drinking water (Figure S3 supplementary data)

There were three studies of total suicide mortality rate where the highest observed lithium level in drinking water was >80µg/l. The random effects meta-analysis showed a statistically significant protective (or inverse) association with a pooled β of -0.20 [95%CI: -0.31, -0.10]; p=0.0002, I^2=0.0%), with no heterogeneity. For the five studies conducted in regions with lithium levels <80µg/l, the pooled β was -0.33 [95%CI: -0.68, 0.01]; p=0.06, I^2=87.0%.

Articles included in the narrative synthesis only (Table S2, supplementary data)

Six articles provided an estimate of the association between lithium levels in drinking water and suicide mortality rates but were not eligible for inclusion in the meta-analysis. Three were additional analyses/reports of the Austrian dataset, which controlled for a variety of additional confounding variables including altitude and rates of lithium prescriptions. Two studies from Japan(23, 34) were conducted in areas which overlapped with the study area for Shiotsuki *et al*(29). There was also a study which compared suicide rates in Texas, USA, counties with relatively high, medium or low lithium concentrations in drinking water(26). All of these studies found statistically significant protective (or inverse) associations between lithium levels and total suicide rates; where data on gender specific rates were presented, protective associations were also found with male suicide rates but not with female suicide rates.

Discussion

This is the first meta-analysis of the ecological association between the lithium levels/concentration in publically available drinking water and the incidence of suicide. We found a consistent protective (or inverse) association between lithium levels and total, male and female suicide mortality rates, which was statistically significant for total and female suicide rates. Similar protective association was observed in the six studies included in the narrative synthesis, and in the subgroup meta-analyses based on the higher/lower suicide mortality rates (≥10 per 100,000, <10 per 100,000) and lithium levels (>80µg/l, <80µg/l). These finding suggest that naturally occurring lithium in drinking water may have the potential to reduce the risk of suicide and may possibly help in mood stabilisation, particularly in populations with relatively high suicide rates and geographical areas with a greater range of lithium concentration in the drinking water.

Strengths and limitations

To our knowledge, this is the most comprehensive synthesis of the ecological association between lithium levels/concentration in publically available drinking water and suicide mortality rates. The main limitations of the epidemiological ecological studies are that they are observational and subject to the ecological fallacy (or ecological bias). Ecological studies are essentially conducted to generate hypotheses. They compare aggregate exposure (e.g. population exposed to lithium levels in drinking water) and disease/health outcome (e.g. suicide mortality rate in the exposed population) across different populations over the same time period or within the same population over time. They are subject to confounding as information on potential confounder(s) may not be available, and associations at the population level do not necessarily represent associations at the individual level (ecological fallacy). Populations may also differ with regard to ethnic, religious, and social class distribution, prevalence and management of mental disorders, and mobility patterns. As with all systematic reviews and meta-analyses, our study can also be subject to reporting/publication bias. These biases arise when the dissemination of research finding is influenced by the nature and direction of results – statistically significant "positive" results are more likely to be published and cited, whereas non-statistically significant results may be filtered, manipulated, or presented in such a way that they become/seem positive. We were unable to conduct a formal assessment of possible publication bias as our meta-analyses did not meet a key assumption (i.e. a minimum of 10 studies) for the tests of funnel plot asymmetry.

Although most of the studies were assessed to be of good quality using our adapted criteria, and our results were unaltered on excluding the two studies judged to be of lower quality, no standardized criteria for quality assessment of ecological studies were available. The studies varied widely in the range of years for which the suicide rates were measured, and in the number and timing of drinking water samples taken. Some of the studies utilised drinking water samples and suicide data from different time periods, thus relying on the assumption that lithium levels do not fluctuate substantially over time. In a study from Japan, Ohgami et al.(34) found negligible change in lithium levels in drinking water when they repeated the measurements after one year. A recent study from Denmark also found little variability over time in lithium levels collected from groundwater between 1947 and 2012(35). However, additional evidence on stability over time of lithium levels in drinking water is needed from other geographical areas.

In a nationwide closed (or non-dynamic) historical (or retrospective) cohort study published in 2017, Knudsen et al(35) linked individual-level register-based data on the entire Danish adult population (3.7 million individuals) from 1991 to 2012 with a moving five-year time-weighted average lithium exposure level from drinking water. Cases of suicides were identified through the Danish Register of Causes of Death, and lithium levels in drinking water were ascertained from 158 water samples obtained from 151 public waterworks supplying approximately 42% of the Danish population. Of these, 139 samples were collected via a drinking water sampling campaign during April-June 2013 (spatially covering the entire country), and 19 samples were collected via a separate campaign at the Greater Copenhagen Utility during October 2009-June 2010. The lithium levels were measured at a single point in time (i.e. cross-sectional) and it was assumed that they had remained constant over the 22-year study period from 1991-2012. The mean lithium level in the drinking water samples was 11.6 µg/L (range, 0.6 to 30.7µg/L). The overall national suicide rate decreased 38% during the study period – from 29.7/100,000 in 1991 to 18.4 per 100,000 in 2012. The spatial regression analysis was adjusted for confounding factors (including gender, age, employment/civil status, and calendar year). The study found no statistically significant association between increasing five-year time-weighted average lithium levels and decreasing suicide rate – although all the incidence rate ratios were ≤1. The authors concluded that there does not seem to be a protective effect of exposure to lithium on the incidence of suicide with levels below 31 µg /L in drinking water. They also noted that in the previous (i.e. ecological) studies that found a significant protective association, the lithium exposure levels were relatively much higher than those found in their study, and the lack of variation in lithium levels in their study may have 'challenged' their analyses. The authors acknowledged that the study had several limitations as it was based on a single cross-sectional measurement of lithium levels from 151 waterworks supplying approximately half of the Danish population; and suggested that future studies could prospectively determine lithium levels from more waterworks on regular basis for a number of years. It is, nevertheless, challenging that the only published study linking exposure to lithium in drinking water with suicide on an individual level was negative.

It has been suggested that the association between lithium in drinking water and suicide might be modified by the rate of lithium prescriptions in the population, as excreted lithium might find its way into the water supply. However, Helbich et al.(32) found no evidence that the rate of lithium prescriptions in an area impacted on the association between lithium levels in drinking water and suicide rates (either directly or via an effect on the mean lithium level in water)(33). It is also noteworthy that some vegetables, grains/nuts, meat and spices are also rich in lithium, but it is difficult to measure dietary lithium as the content is variable and relates to lithium content in water/soil. It is therefore likely that lithium intake from food will be relatively higher in areas which have high lithium content in water(10, 36, 37). It has been estimated that average daily intake of lithium from food by adults in the US range from 650 to 3100µg, whereas in areas of Texas with unusually high lithium levels the contribution from drinking water might be around 340µg(10). The association between exposure to dietary lithium and incidence of suicide has not been investigated. Furthermore, bottled drinking water (processed/treated or natural mineral water from spring) often has much higher lithium content than tap water – the association between exposure to lithium via bottled water and suicide has not been studied.

Possible mechanism(s) behind the association between lithium in drinking water and suicide

A possible mechanism by which lithium in drinking water might prevent suicide is by ameliorating the symptoms of mood disorders. In a randomised controlled trial of former drug users a 400µg daily dose of lithium was found to improve mood with peak effect after 4 weeks of administration(9). There may also be a cumulative effect of sustained low-dose exposure over longer time periods, as lithium levels in drinking water have been shown to correlate with serum levels of lithium in areas of high water lithium(38). There is little information on the association between lithium in drinking water and the prevalence and severity of mood disorders. In a population-based nested case-control study from Denmark, higher long-term lithium exposure from drinking water was not associated with a lower incidence of mania/bipolar disorder – suggesting that long-term exposure to micro doses of lithium does not modulate the risk of these conditions(39). On the other hand, in an another population-based nested case-control study by the same research group, higher long-term lithium exposure from drinking water was associated with a lower incidence of dementia in a nonlinear way(40).

It is also possible that trace doses of lithium might reduce suicide rates via its anti-aggressive effects. Therapeutic/pharmacological doses of lithium have been found to reduce aggressive/violent behaviour in a variety of populations(41), and inverse associations have been observed between lithium levels in drinking water and rates of violent crimes(26, 42). Similarly, a recent cross-sectional study of adolescents in Kochi prefecture in Japan found an inverse association between lithium content of drinking water available to schools and interpersonal violence and depressive symptoms among adolescents(43). As violent methods of suicide are more likely to be lethal, lithium ingestion might be expected to reduce the lethality of suicide attempts. This was observed in a recent meta-analysis of the effects of long-term lithium treatment of patients with major affective disorder, where the incidence ratio of attempts-to-suicides increased 2.5 fold with lithium treatment, indicating a considerably reduced lethality(44). The meta-analysis also showed that the risks of completed and attempted suicide were consistently lower (by about 80%) in patients with bipolar and other major affective disorders treated with pharmacological doses of lithium for an average of 18 months.

Conclusions and recommendations for future research

In summary, this meta-analysis and narrative synthesis of ecological studies suggests that there is a protective (or inverse) association between lithium levels/concentration in publically accessible water supply and suicide mortality at the population level. As discussed above, ecological studies are excellent for generating hypotheses, but cannot establish causality due to inherent confounding and ecological fallacy. It has been suggested that randomised community trials of lithium supplementation of the water supply might be a possible means of testing the hypothesis, particularly in communities (or settings) with demonstrated high prevalence of mental health conditions, violent criminal behaviour, drug-dependency and chronic substance abuse and risk of suicide. This may provide further evidence to support the hypothesis that lithium could be used at the community/population level to reduce or combat the risk of these conditions. It may also be possible to measure lithium levels in people who report to A&E with self-harm/suicidal ideation and at inquest for suicide. The synthesized evidence suggests that the protective (or inverse) association between lithium levels in drinking water and suicide mortality rates is likely to be stronger in populations with relatively higher suicide mortality rates. Future studies might benefit by concentrating on areas with a wide range of lithium levels/concentration in drinking water and relatively high suicide mortality rates and would ideally also consider the effect and levels of dietary lithium from food sources.

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Declaration of interests

AHY has received payment for lectures and advisory board membership from AstraZeneca, Eli Lilly, Lundbeck, Sunovion, Servier, Livanova, and Janssen and reports no shareholdings in pharmaceutical companies. He is the lead investigator for the Embolden Study (AZ), BCI Neuroplasticity Study, and Aripiprazole Mania Study, and has led investigator-initiated studies from AstraZeneca, Eli Lilly, Lundbeck, Wyeth, and Janssen. RS has received an honorarium for speaking at a Lundbeck-sponsored event. The authors are aware of no other conflicts of interest.

Author contributions

AM conceived and designed the study. IR, SF and AM did the literature search and quality assessment of included studies. IR and SF selected the studies and extracted the relevant information. IR and AM synthesised the data. AM and IR wrote the manuscript. BC, RS, DH-M and AHY critically reviewed the manuscript for intellectual content. All authors approved the final version of the manuscript for publication. AM guided and supervised the overall work.

Table 1. Characteristics of studies included in the systematic review and meta-analysis

Study	Region and number of locations	Population data	Number of lithium samples; dates and methods of collection; analysis method	Lithium levels in µg/l Mean (range)	Mean suicide rate (per 100,000/y)	SMR mean (range)	Covariates	Statistical methods and results
Kabacs et al. 2011(14)	East of England, 47 subdivisions	All suicides 2006-2008 (total population 5,700,000)	47 samples; collected from publically accessible water sources; analysed using mass spectrometry	4.98* (<1 – 21)	NR	T:98 (36 – 194) M 95 (35 – 213) F 108 (0 – 292)	None	Pearson correlation between lithium and SMR T: r = -0·03, p = 0·838 M: r = -0·054, p = 0·715 F: r = 0·042, p = 0·777 Population weighted least squares regression of SMR on Log Li (µg/l) T: β (se) = -0·062 (0·145)[†] M: β (se) = -0·059 (0·143)[†] F: β (se) = -0·036 (0·147)[†]
Kapusta et al. 2011(28)	Austria, 99 districts	All suicides 2005-2009 (total population 8,297,964)	6460 samples; 2005-2010, samples of local drinking water; analysed by inductively coupled plasma optical emission spectrometry	11·3 (3·3 – 82·3)	T: 16·5[‡] M: 26·4[‡] F: 7·00[‡]	T: 0·790[‡,§] M: 0·821[‡,§] F: 0·673[‡,§]	Population density, income per capita, proportion of Roman Catholics, unemployment rates, density of GPs, psychotherapists and psychiatrists	Population weighted least squares regression of SMR on Log Li (µg/l) Unadjusted analyses T: β = -0·22, p = 0·029 M: β = -0·18, p = 0·083 F: β = -0·21, p = 0·037 Adjusted analyses T: β = -0·243, p = 0·022 M: β = -0·19, p = 0·062 F: β = -0·22, p = 0·088

Study	Region and number of locations	Population data	Number of lithium samples; dates and methods of collection; analysis method	Lithium levels in µg/l Mean (range)	Mean suicide rate (per 100,000/y)	SMR mean (range)	Covariates	Statistical methods and results
Blüml et al. 2013(30)	USA, Texas, 226 counties	All registered suicides 1999-2007 (total population NR)	3123 samples; 1999-2007, collected for Texas Water Board from public wells; NR	46·3‡ (2·8 – 219·0)	13·16‡	NR	Population density, age, proportion of females, African Americans, Hispanics and Latino Americans median income per household, poverty, unemployment	Population weighted linear regression of age-standardized suicide rate on Log Li T: β (se) = -0·04 (0·02), p < 0·01
Giotakos et al. 2013(24)	Greece, 34 prefectures	All registered suicides 1999-2010 (total population NR)	149 samples; collected 2012; analysed by mass spectrometry	11·10 (0·1 – 121)	NR	NR	None	Linear regression of age-standardized suicide rate on Li (µg/l) T: β = -0·02, p < 0·05, t = -2·10
Sugawara et al. 2013(16)	Japan, Aomori prefecture, 40 municipalities	All registered suicides 2008-2010 (total population 1,373,339)	NR; NR; analysed by mass spectrometry	NR (0·0 – 12·9)	NR	M: 123 (96 – 186) F: 105 (72 – 152)	density of medical institutions, unemployment rate	Population weighted least squares regression of SMR on Log Li Unadjusted analyses M: β = 0·136, p = 0·408 F: β = -0·350, p < 0·05

Study	Region and number of locations	Population data	Number of lithium samples; dates and methods of collection; analysis method	Lithium levels in µg/l Mean (range)	Mean suicide rate (per 100,000/y)	SMR mean (range)	Covariates	Statistical methods and results
								Adjusted analyses M: β = 0·064, p = 0·777 F: β = -0·369, p <0·10
Pompili et al. 2015(25)	Italy, 145 cities	All suicides in ages >15 1980-2011, except 2004/2005 (total population 17.2 million in 2000-2011)	157 samples; 2009-2010; analysed by mass spectrometry by third party as part of a separate geochemistry research project	5·28 (0·11 – 60·8)	2000-2011: 7·53	NR	Mountainous, urbanized, south of Rome	Population weighted least squares regression of SMR on Log Li 2000-2011: Unadjusted analyses T: β < 0·001, p = 0·997 M: β = 0·046, p = 0·581 F: β = -0·134, p = 0·109 Adjusted analyses T: β = 0·079. p = 0·308 M: β = 0·107, p = 0·159 F: β = -0·032, p = 0·703 1990-1999: Unadjusted analyses T: β = -0·047, p = 0·578 M: β = -0·009, p = 0·915 F: β = -0·165, p = 0·047 Adjusted analyses T: β = 0·079, p = 0·323 M: β = 0·087, p = 0·280 F: β < 0·001, p = 0·998

Study	**Region and number of locations**	**Population data**	**Number of lithium samples; dates and methods of collection; analysis method**	**Lithium levels in µg/l Mean (range)**	**Mean suicide rate (per 100,000/y)**	**SMR mean (range)**	**Covariates**	**Statistical methods and results**
								1980-89: Unadjusted analyses T: β = -0·234, p = 0·005 M: β = -0·161, p = 0·053 F: β = -0·339, p < 0·001 Adjusted analyses T: β = -0·044, p = 0·560 M: β = 0·013, p = 0·859 F: β = -0·154, p = 0·043
Shiotsuki et al. 2016(29)	Japan, Hokkaido Island and Kyushu Island, 153 cities	All suicides from cities only in 2010/2011 (total population 16,981,717)	NR; 2010-2015, samples collected from rail stations and city offices; analysed by mass spectrometry	3·8 (0.1 – 43)	T: 23·8 M: 35·7 F:13·1	T: 111·2 (sd 31·6) M: 119·1 (sd 38·6) F: 97·1 (sd 44·9)	Annual mean temperature, total sunshine, total rainfall and total snowfall	Population weighted least squares regression of SMR on Log Li Unadjusted analyses T: β = -0·153, p = 0·059 M: β = -0·225, p = 0·005 F: β = -0·012, p = 0·883 Adjusted analyses T: β = -0·129, p=0·070 M: β = -0·164, p = 0·037 F: β = 0·014, p = 0·870
Liaugaudaite et al. 2017(27)	Lithuania, 9 cities	All suicides 2009 -2013 (total	22 samples; collected Nov 2013 – Jan 2014; analysed	10·9 (0·48 – 35·53)	T: 27 (range 16-50) M : 51(range 29-93)	NR	Female: male ratio of city population	Population weighted least squares regression of log Li on age-standardized suicide rate

Study	Region and number of locations	Population data	Number of lithium samples; dates and methods of collection; analysis method	Lithium levels in µg/l Mean (range)	Mean suicide rate (per 100,000/y)	SMR mean (range)	Covariates	Statistical methods and results
		population 1,109,261)	by mass spectrometry		F: 7(range 0-13)			Unadjusted analyses T: β (se) = -0.911 (0.156)‖ M: β (se) = -0.965 (0.100)‖ F: β (se) = 0.150 (0.374)‖ Adjusted analyses T: β = -0·283, p = 0·034 M: β = -0·702, p = 0·013 F: β = 0·253, p = 0·523
Palmer et al. 2018(13)	USA, Alabama, 15 counties	Average suicide rate from 1999-2013 in selected Alabama counties (total population NR)	75 samples; collected May 2016 from public locations; analysed by plasma emission spectrophotometry	NR (0·4 – 32·9)	NR (range 3·3 – 22·0)	NR	None	Spearman's correlation of age-standardized suicide rate against lithium levels T; r = -0·6286, p = 0·0141 M: r = -0·625, p = 0·0148 F: r = -0·4393, p = 0·1032 Linear regression of SMR on Log Li Unadjusted analyses T: β (se) = -0·6188 (0·2179)¶ M: β (se) = -0.6236 (0·2168)¶ F: β (se) = -0·4387 (0·2427)¶

NR – not reported * Personal communication from Nikolett Kabacs, † Calculated from data supplied by Nikolett Kabacs, ‡ Personal communication from Nestor Kapusta, § SMR has reference 1.00 not 100, ‖ Standard errors from personal communication from Vilma Liaugaudaite, ¶ Calculated from data supplied by Greg Gorman. T= total (i.e. both sexes combined), M=male. F=female.

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Figure 1. PRISMA flow diagram for study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis

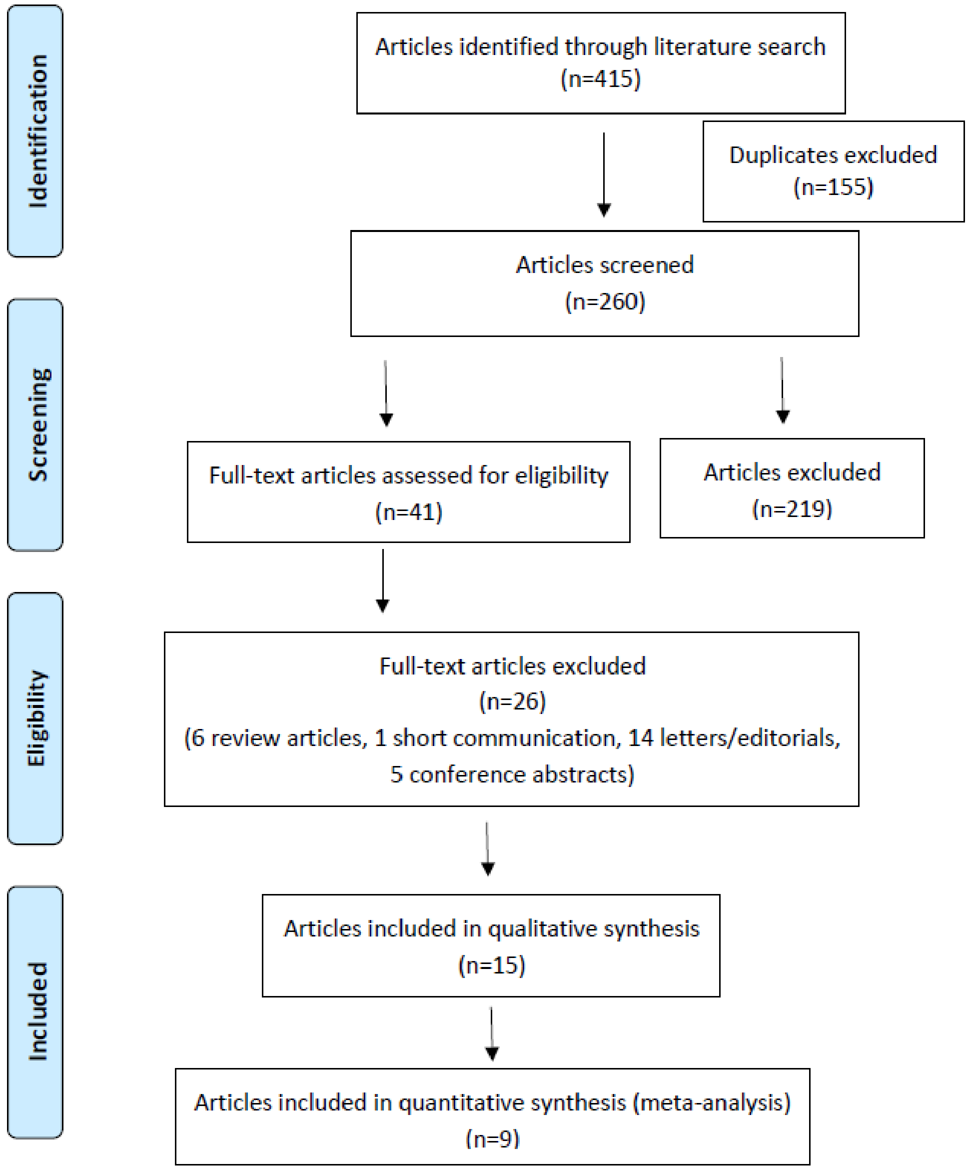

Figure 2: Random effects meta-analysis of the association between lithium concentration in drinking water and total suicide rates. Standardised regression coefficients (Beta) for each study are presented as squares, with the position of the square corresponding to the Beta and the 95% confidence interval (95% CI) shown by horizontal lines. 95% CIs for each study shown in the forest plot are obtained by back transformation using the calculated standard error used in the analysis and do not always conform exactly to the stated confidence intervals in the paper. The area of the square is inversely proportional to the variance in Beta. The diamond represents the pooled Beta and corresponding 95% CI.

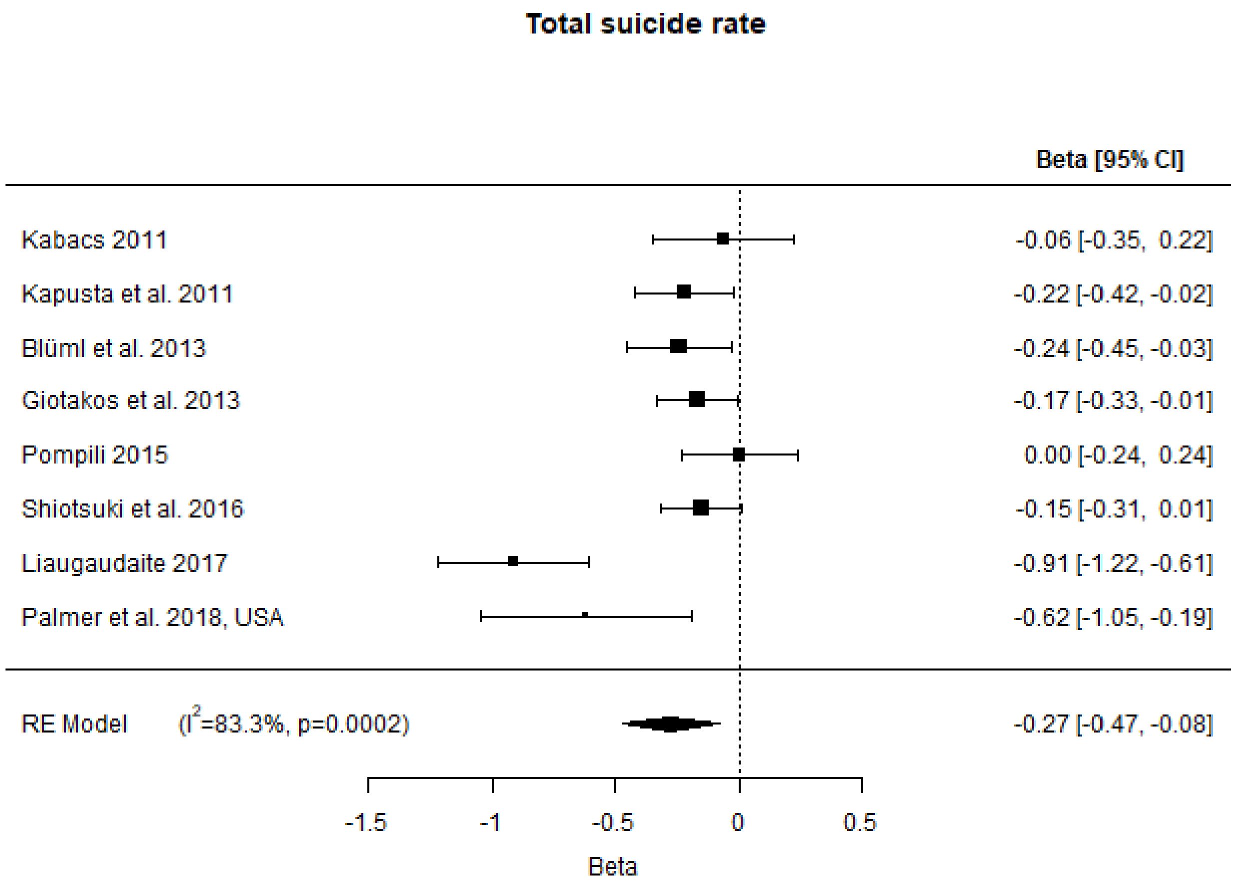

Figure 3: Random effects meta-analysis of the association between lithium concentration in drinking water and male suicide rates. Standardised regression coefficients (Beta) for each study are presented as squares, with the position of the square corresponding to the Beta and the 95% confidence interval (95% CI) shown by horizontal lines. 95% CIs for each study shown in the forest plot are obtained by back transformation using the calculated standard error used in the analysis and do not always conform exactly to the stated confidence intervals in the paper. The area of the square is inversely proportional to the variance in Beta. The diamond represents the pooled Beta and corresponding 95% CI.

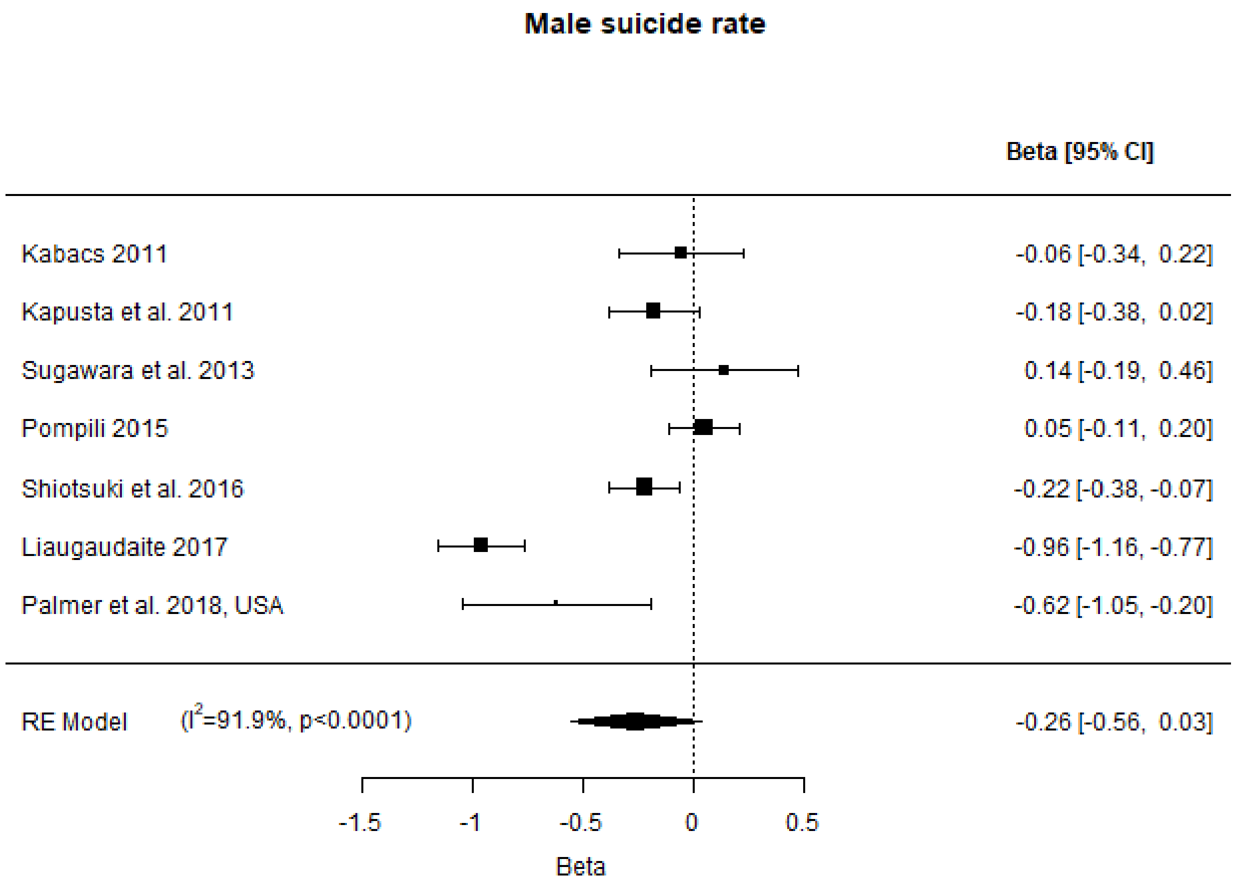

Figure 4: Random effects meta-analysis of the association between lithium concentration in drinking water and female suicide rates. Standardised regression coefficients (Beta) for each study are presented as squares, with the position of the square corresponding to the Beta and the 95% confidence interval (95% CI) shown by horizontal lines. 95% CIs for each study shown in the forest plot are obtained by back transformation using the calculated standard error used in the analysis and do not always conform exactly to the stated confidence intervals in the paper. The area of the square is inversely proportional to the variance in Beta. The diamond represents the pooled Beta and corresponding 95% CI.