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Psychiatric benefits of lithium in water supplies may be due to protection from the neurotoxicity of lead exposure

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ABSTRACT

Introduction: Lithium is a medication used to treat bipolar disorder and may also prevent cognitive decline and suicide. Lithium is also found naturally, in levels well below clinical doses, in drinking water worldwide, and levels have been inversely associated with rates of psychiatric disorders. Lead (Pb) is another element in the environment but is a toxin of public health concern. Negative effects of chronic lead exposure and possible benefits of environmental lithium exposure appear complementary.

Hypothesis: Exposure to environmental lithium has associated benefits, which may be due to the mitigation of lead toxicity by lithium.

Methods: A series of reviews tested each element of the hypothesis. A systematic review clarified the psychiatric and medical correlates of lithium in drinking water. Non-systematic reviews clarified the harms of environmental lead, summarized experimental studies of lithium used to prevent lead toxicity, and explored overlapping biological mechanisms in lithium and lead exposure.

Results: Higher levels of lithium in drinking water were associated with lower suicide rates in 13 of 15 identified studies. While fewer studies were available for other outcomes, lithium was associated with lower rates of homicide, crime, dementia, and mortality. Lead was reported to be ubiquitous in the environment, and chronic low-level exposure has been associated with adverse effects, including effects opposite to the outcomes associated with lithium. Animal studies demonstrated that lithium pre-treatment mitigates lead toxicity. Neurophysiological correlates of lead and lithium exposure overlap.

Conclusions: Microdose lithium is associated with better psychiatric and medical outcomes, which are complementary to harms of environmental lead exposure. Experimental animal evidence is supportive, and lead and lithium impact overlapping neurophysiologic pathways. Therefore, several lines of circumstantial evidence suggest that lithium protects against the neurotoxic effects of lead. Further studies are required to clarify the benefits and mechanisms of low-dose lithium. There are significant public health implications if this paper's hypothesis is true.

Introduction

Lithium, the third element on the periodic table, is an established medication. It is a mood stabilizer: a first-line treatment for bipolar disorder [1], and it is also used in unipolar depression. Treatment with lithium reduces the risk of suicide across psychiatric diagnoses, with high quality evidence in bipolar disorder and unipolar depression [2]. Clinically, typical doses may range from 600 mg to 1800 mg per day and individual doses are based on clinical effect, side effects, and blood levels [3,4]. At lower doses, lithium may also reduce the progression to dementia from mild cognitive impairment [3].

Not only found in the medicine cabinet, lithium is abundant in the Earth's crust. Present in minerals in varying amounts in different regions, lithium dissolves into groundwater and is commonly found in drinking water. In turn, lithium is consumed by humans who drink the water and eat the grains and vegetables that take it up [5]. Daily intake of lithium therefore ranges by location and diet, with estimates of mean daily intake in the range of 348–1560 μg/day (0.348–1.560 mg/day) [5], i.e. two to three orders of magnitude lower than effective clinical doses (see Fig. 1 for visualization).

Nonetheless, mounting evidence from epidemiological studies that correlate drinking-water lithium levels with health outcomes suggests that exposure to microdose environmental lithium may be beneficial. For example, higher drinking water concentrations are shown to

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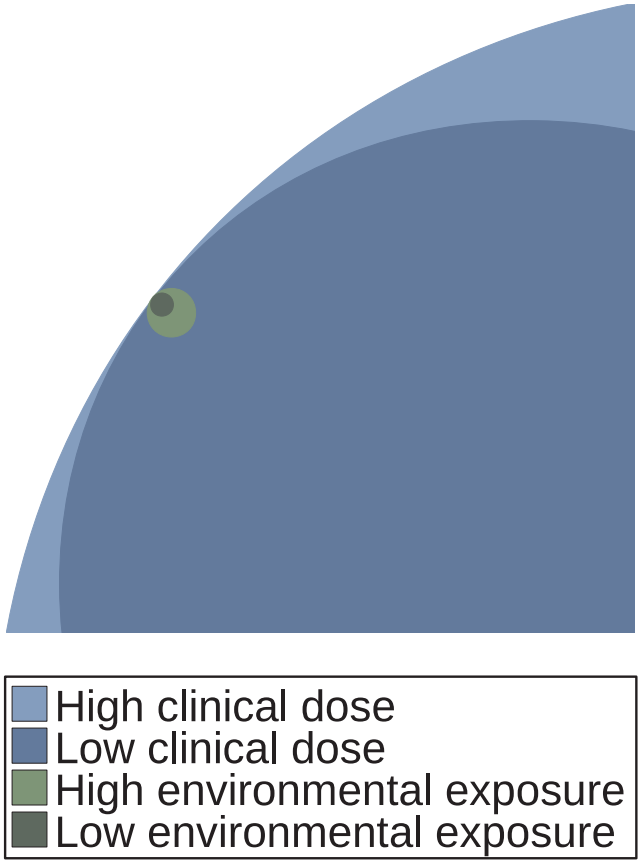

Fig. 1. Relative size comparisons of clinical lithium doses[3] compared to estimated mean environmental daily intake[5], represented with dose proportional to circle areas.

correlate with lower rates of suicide, homicide, and dementia [6,7].

Despite its status as an established effective medication, the mechanism underlying the clinical benefits of lithium is uncertain [8]. Lithium has broad effects on cellular signalling pathways in the brain involving glycogen synthase kinase 3 (GSK-3), cyclic adenosine monophosphatase response element binding protein (CREB), and Na^+-K^+ adenosine triphosphatase (ATPase), with influences on calcium homeostasis [8]. The beneficial mechanism of action may differ in different populations [8]. As with bipolar disorder, the mechanism of the purported beneficial effects of microdose lithium is uncertain [3].

Meanwhile, lead is described as ubiquitous in the environment in varying amounts, detectable even in regions of the arctic [9]. Lead is noted to be a "cumulative general poison", and is neurotoxic [9]. The Centre for Disease Control reports that for children, no safe lower limit of lead blood level has been found [10]. Lead toxicity is a global public health problem: 0.2% of deaths and 0.6% of disability-adjusted life years are attributed to lead exposure, surpassing urban outdoor air pollution and climate change [11].

Hypothesis

A parsimonious mechanistic explanation of the effects of microdose lithium would account for the breadth of its apparent effects. A possible clue to that mechanism may be in the broad and complementary effects of lead, another environmental element. We hypothesize that if the harms of lead exposure are opposite to the benefits of lithium exposure, then the benefits of lithium may be due to mitigation of the toxicity of lead. This possibility is important to clarify, as it would have implications on any recommendations to supplement lithium.

The hypothesis would be supported if: the harms of lead are opposite to the benefits of lithium; lead and lithium co-occur in the environment where such harms and benefits are observed; lead and lithium have effects on shared biological processes; there is experimental evidence demonstrating lithium mitigates the neurotoxicity of lead. The aim of this paper is to review the literature for evidence supporting or refuting these empirical possibilities in order to clarify the relationship and determine the next steps that may be required.

Methods

This paper aims to explore the hypothesis that lithium mitigates the negative health impacts of lead. First, in Part 1, a systematic review was done to identify the health outcomes associated with environmental lithium exposure. Second, in Part 2 the health risks of lead exposure were reviewed. Third, potential causal connections between lithium and lead were identified by reviewing experimental studies (Part 3). And finally, potential areas of overlap in the mechanisms of action in lithium and lead were identified by highlighting physiologic and biologic studies (Part 4).

Part 1: Systematic review of the health impacts of exposure to environmental lithium

Literature search

A systematic search was completed using MEDLINE with the PubMED interface on November 16, 2017 with the following query: ((“lithium”[MeSH Terms] OR “lithium”[All Fields]) AND (“water”[MeSH Terms] OR “water”[All Fields] OR “drinking water”[MeSH Terms] OR (“drinking”[All Fields] AND “water”[All Fields]) OR “drinking water”[All Fields])). The human filter was applied. By using the human filter, articles that have not yet been indexed with MeSH subheadings are excluded, so there is a risk of missing the most recently published articles. Therefore, the search was repeated without the filter to identify potential recent articles from January 1, 2017 to November 16, 2017. These articles were combined with the first search and duplicates removed.

Entries were included if they described a peer-reviewed, primary literature study that reported on a direct or indirect measure of drinking water lithium and a psychiatric or non-psychiatric medical outcome. The rationale for considering all health outcomes is the arbitrary distinction between mental and medical illness, as well as the potential impact of medical problems on illnesses categorized as psychiatric (for example the impact of thyroid diseases on mood disorders and vascular disease on cognitive disorders). Entries were excluded if they did not contain an abstract; were not in English; or were reviews (which were separately retrieved for background and to identify any missed primary articles), commentaries, letters, or hypotheses if they did not contain original data. Interventional studies that administered lithium as a treatment were excluded.

Part 2: What are the psychiatric impacts of environmental lead exposure?

Compared to the potential benefits of exposure to environmental lithium, lead toxicity is an established fact in the medical and scientific literature and a topic of great importance to public health. Therefore, for efficiency and accuracy, Part 2 relied on previously-published, recent high-quality reviews. A non-systematic search for recent scoping reviews from governmental and non-governmental bodies such as the World Health Organization (WHO) and the government of Canada was completed. The reviews were read and summarized to answer specific questions relating to the hypothesis. When there was insufficient information in the identified reviews, primary source literature was used to answer the question and critically appraise the articles individually.

Is lead present in the environment where benefits of lithium have been suspected?

If exposure to lithium through drinking water reduces the risk of mental and physical health conditions, and if the mechanism is by mitigating harm from environmental lead exposure, then it is necessary but not sufficient that environmental lead exposure be associated with conditions in which drinking-water lithium is purported to have benefits. To answer this question, the reviews of environmental lead toxicity were summarized, and articles found in the systematic search from Part 1 were reviewed to identify whether they also included a measure of lead exposure.

Is exposure to lead associated with effects opposite to the effects associated with lithium in humans?

If lithium mitigates the toxic effects of lead, then the effects of lead should be opposite to those associated with lithium. As lead toxicity cannot be evaluated by randomized controlled trial, large, well-designed, well-controlled observational studies are best suited to answer these questions. Subsequent to identifying the associated effects of lithium, the effects of lead were noted on the basis of the available reviews, and where information on a specific effect was missing from the identified reviews on lead, a targeted literature search was completed, and the identified articles were critically appraised.

Part 3: Does lithium exposure protect against lead toxicity?

Experimental methods such as randomized controlled trials are the gold-standard design to ascertain causality. A literature search identified experimental studies (including animal studies), which demonstrate causality, where lithium has been used to mitigate lead exposure. A PubMed search was conducted using the following query: ("lithium"[MeSH Terms] OR "lithium"[All Fields]) AND ("lead"[MeSH Terms] OR "Pb"[All Fields]).[1] Additional articles were retrieved by checking the citations of previously identified articles and with additional specific searches.

Part 4: Biological mechanisms

Systematically reviewing the basic science literature that explores pharmacological and physiological mechanisms of lithium and lead is beyond the scope of this report. Therefore, recent reviews and targeted searches were used to identify and illustrate possible mechanisms by which lithium and lead may interact, which would be consistent with the hypothesis that lithium alters the effects of lead.

Results of reviews

Part 1: Health effects of environmental lithium exposure

The results of the systematic review are summarized in a PRISMA [12] diagram (Fig. 2). The initial search produced 3195 entries, which was reduced to 822 by application of the human filter. An additional 194 recent abstracts were identified, for a combined 1006 unique entries to review. Based on the above inclusion and exclusion criteria following review of the titles and abstracts, 60 abstracts were included and 946 excluded. Of the 60 abstracts, 56 full articles were retrievable.[2] Following retrieval, articles were read, and 32 articles met inclusion criteria.

A systematic review completed in August 2013 identified 11 epidemiologic studies of trace lithium doses [6]. Ten of these were identified by the above search. A systematic review of environmental lithium and suicide identified 9 studies in a search completed in December 2013 [7]. All 9 were captured by the above search.

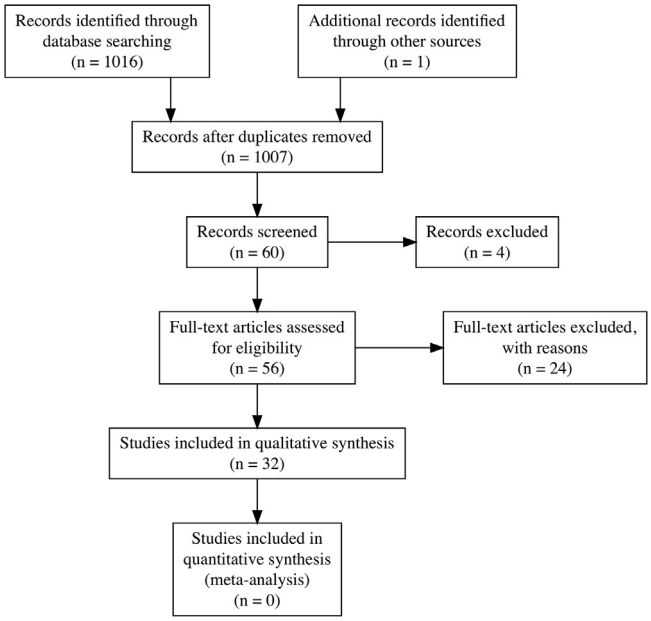

Fig. 2. Results of systematic review of health impacts of environmental lithium.

The 32 primary literature studies identified were categorized based on the health outcome: suicide, homicide, dementia, other psychiatric effects, and non-psychiatric medical effects.

Suicide

Of the 32 articles, 15 publications tested the association between suicide rates and lithium levels measured in drinking water using 12 unique samples, as 4 publications reported different analyses of the same data set [13–16]. The articles are summarized in Table 1. All studies reported on rates of suicide to test for an effect of levels of lithium in drinking water. The studies cover countries from 3 continents: Austria, England, Greece, Denmark, Lithuania, Italy, Japan, and the United States.

Only 2 of the 15 studies did not identify any relationship between lithium level and suicide. The two negative studies were from England [17] and Denmark [18] where the range of drinking water lithium was found to be low (0–21 μg/L and 0.6–30.7 μg/L respectively).

Six studies used covariates to account for potential confounds that may impact suicide rates. Controlling for sociodemographic covariates did not account for the effect of lithium in the studies identified. However, one study used altitude as a covariate [15] and found that overall higher lithium is associated with lower suicide, but that the relationship was reversed in areas of high altitude, and cited previous research that had associated altitude with suicide rates.

In their previous systematic review, Vita et al. [7] concluded that drinking water lithium may be associated with a reduced risk of suicide. Since that publication, there have been an additional 6 studies of suicide risk, of which only one did not find an association [18].

Sex differences in the association of drinking water lithium and suicide were described. In subgroup analyses, several papers reported a negative association in men and a weaker or no association in women [4,13,19–21], whereas only one study saw a possible association in women and no association in men [22]. More frequent use violent means of suicide among men has been proposed as an explanation for the observed sex differences [4,19,21], with lithium suspected to reduce suicide via reduction of violence and aggression [23].

[1] The word "lead" has homonyms that make its use as a non-MeSH search term impractical.

[2] Full text versions for 4 older studies (1970–1988) were not retrievable and were therefore excluded.

Table 1
Studies that report on the association between suicide rates and environmental lithium.

First Author, Citation	Location Years	Mean (SD) lithium (μg/L)	Covariates	Result
Year of publication	Water samples	Lithium range (μg/L)		
Helbich [13] 2015	Austria 2005–2009 6460 samples (the same sample was used by all 4 studies)	10 (10) 3 > 16	Lithium prescription	Higher lithium associated with lower incidence of suicide overall, among males only, but not in female subgroup; no impact of lithium prescription
Helbich [15] 2013		10 (11) –	Altitude, population density, income, religion, psychiatrists, psychotherapists and general practitioners per capita, unemployment	Higher lithium associated with lower incidence of suicide in lower altitudes, and higher incidence of suicide in higher altitudes
Helbich [14] 2012		11.3 (27) 0–82.3		Higher lithium associated with lower incidence of suicide
Kapusta [16] 2011		11.3 (27) 0–82.3		Higher lithium associated with lower incidence of suicide
Bluml [64] 2013	Texas (254 counties) 1999–2007 3123 samples	– 2.8–219.0	Unemployment, population density, income, ethnicity	Higher lithium associated with lower incidence of suicide
Giotakos [26] 2013	Greece (34 of 52 prefectures) 1999–2010 149 samples	11.1 (21.16) 0.1–121		Higher lithium associated with lower incidence of suicide
Ishii [60] 2015	Japan (Kyushu island) 2010–2013 434 samples	4.2 (9.3) 0–130	Proportion of elderly people, 1-person households, education, industrial employment, unemployment, marriage rate, temperature, annual postal savings	Higher lithium associated with lower incidence of suicide overall, among males only, but not in female subgroup
Kabacs [17] 2011	England (East, 43 suburbs) 2006–2007 47 samples	– < 1–21		No statistically significant association
Knudsen [18] 2017	Denmark 1991–2012 151 samples	11.6 (6.8) 0.6–30.7		No statistically significant association
Liaugaudaite [4] 2017	Lithuania (9 cities) 2009–2013 22 samples	10.9 (9.1) 0.48–35.53		Higher lithium associated with lower incidence of suicide in men but not women
Ohgami [61] 2009	Japan (Oita prefecture) 2002–2006 18 samples	– 0.7–59		Higher lithium associated with lower incidence of suicide in total, in men and marginally significant in women
Pompili [65] 2015	Italy 1980–2011 157 samples	5.28 0.11–60.8		Mixed results: Higher lithium associated with lower incidence of suicide in 1980–1989 decade, but not later decades
Schrauzer [24] 1990	Texas 1978–1987 2–5 per county (27)	– 0–160		Lower suicide, homicide and violent crimes in counties with higher lithium
Shiotsuki [63] 2016	Japan (Hokkaido and Kyushu) 2010–2011 153 samples	3.8 (5.3) 0.1–43	Meteorological data	Higher lithium associated with lower incidence of suicide in men but not women
Sugawara [64] 2013	Japan (Aomori prefecture) Unreported. Multiple samples per 40 municipalities.	– 0–12.9	Medical institutions, unemployment	Higher lithium associated with lower incidence of suicide in women but not men, no longer significant with co-variates

Homicide

Two studies reported on the association of drinking water lithium and homicide, one of which also investigated suicide and also appears in Table 1 [24]. In this study, 27 Texas counties were grouped based on levels of lithium in the drinking water (0–12, 13–60, and 70–160 μg/L) and group differences in suicide and crime rates were compared with t-tests. With respect to homicide, the counties with the highest levels of lithium had the lowest homicide rates (7.5 per 100,000) as compared to

the medium (13.4 per 100,000) and low (16.9 per 100,000) lithium counties which was statistically significant.

More recently, Giotakos et al. [25] reported higher drinking water lithium levels to be associated with lower homicide rates when looking at the same 34 Greek prefectures as in the group's earlier study reporting an association with suicide [26]. Using linear regression, there was a statistically significant negative relationship between homicide and drinking water lithium. However, when the analysis was weighted by population, the direction of the relationship remained, but was no longer statistically significant.

Dementia

Two studies reported on rates of dementia. The retrospective population-based study by Kessing et al. is notable for the large sample size (73,731 cases with dementia and 733,653 controls) and long study period (1995–2013) [3]. The group also linked each person's address through the study period to a nationwide map of lithium levels computed from 151 measurements. The incidence rate ratio was calculated for individuals in 4 groups based on mean lithium exposure over the range of 0–27.0 μg/L. The lowest rates of both vascular and Alzheimer's dementia were found in the groups with the highest lithium exposure. However, there was a small but statistically significantly higher rate of dementia in the second-lowest exposure group. The authors acknowledged that unmeasured social or environmental factors could be confounding the results.

Fajardo and colleagues also sought to identify the relationship between drinking water lithium and changes in mortality rates from Alzheimer's dementia [27]. In their 2017 study, they calculated changes in age-adjusted mortality rates from Alzheimer's dementia between 2000–2006 and 2009–2015 for 155 Texas counties. They included extensive covariates that have been linked to dementia including sociodemographic factors as well as pollution, physical activity, obesity and presence of type II diabetes. They had access to 6180 water samples. As expected, they found an overall increase in mortality from Alzheimer's dementia over time: 27%. They also found that higher levels of lithium were negatively correlated with increases in mortality rates. The association remained when controlling for sociodemographic factors but not when physical activity, obesity, and type II diabetes were included in the analysis. They also found a negative association between lithium levels and obesity and type 2 diabetes. A post hoc analysis also showed that in counties with fewer than 20 Alzheimer's-related deaths over the time period, lithium levels were higher.

Other psychiatric effects

In a study of similar design as the group's dementia paper, Kessing et al. also reported on the association of bipolar disorder with drinking water lithium levels and found no association [28].

In the only identified study to specifically look at adolescent mental health, Ando et al. correlated questionnaire responses of 3040 adolescents in Kochi, Japan with drinking water lithium and found a significant negative association with depressive symptoms and violence, but no association with suicidal ideation or self-harm. They used a multivariate regression analysis and included age, sex, size of school, and whether they were living with parents as covariates.

Two studies found that drinking water lithium levels were associated with psychological traits. Matsuzaki and colleagues found that lithium levels were positively correlated with hyperthermic temperament scores and negatively correlated with depressive temperament scores [29]. In the only identified study that measured endogenous lithium levels as a surrogate measure rather than drinking water lithium, Norra et al. found lithium levels to be negatively correlated with emotional lability [30].

In the oldest identified study looking at psychiatric outcomes and drinking water lithium, higher levels of drinking water lithium were associated with lower rates of psychiatric hospital admissions as well as the diagnosis of psychosis, neurosis, and personality disorders in Texas [31].

Non-psychiatric medical effects

Zarse and colleagues looked at the connection between lithium in drinking water lithium and all-cause mortality in Oita, Japan. In 1,206,174 people from 18 municipalities, there was a strong negative correlation between water lithium levels and all-cause mortality [32]. This relationship persisted even after controlling for suicide.

A negative correlation between municipal water lithium levels and atherosclerotic heart disease in Caucasians in American cities was reported [33].

A group from Argentina published 4 studies on the health correlates of environmental lithium exposure [34–37]. They noted that Argentinian Andes mountains are associated with very high levels of drinking water lithium (e.g. up to 1005 μg/L) [34]. They used urinary excretion of lithium as a surrogate measure of environmental lithium exposure and found an association with thyroid function (T4) within a normal range in healthy individuals [34]. In a sample of pregnant women, blood lithium levels were positively correlated with thyroid stimulating hormone [36], negatively correlated with fetal measures and birth weight [37], and associated with levels of vitamin D3, calcium and magnesium [35].

Budd and Rossof [38] were unable to replicate an association of leukemia with drinking water lithium [38]. No association was found between drinking water lithium and the incidence of anencephaly [39].

Part 2: Health effects of environmental lead exposure

The WHO has published extensive background documents and guidelines about lead toxicity, including specifically for drinking water quality [9]. In the WHO report on global health risks, 0.2% of deaths and 0.6% of disability-adjusted life years are attributed to lead exposure, surpassing urban outdoor air pollution and climate change [11]. Given the global scope and severity of the problem, individual countries, including Canada in a detailed 2017 report, [40] have published extensive reviews for consultations and guidelines.

Presence of lead in the environment

All of the locations identified in Part 1, in Europe, America and Asia are affected by environmental lead contamination [9].

A major source of lead in the environment is the global use of leaded gasolines introduced in the 1920s, with consumption peaking in the 1970s, and currently phased out in most countries [9,41]. As a result, concentrations of lead in the air and environment vary depending on location and year [9]. For example, in Canada, mean air concentration at measuring stations decline from 0.74 to 0.10 $\mu g/m^3$ from 1973 to 1989 [9]. The WHO notes that water has become the "largest controllable source of lead exposure in the USA", as a result of mineral dissolution and plumbing systems [9]. In addition to air and water contamination, humans are significantly exposed to lead through paint, dust, soil and food [9].

As the toxic effects of lead are both acute and cumulative, present as well as past lead contamination is relevant for present health concerns. For example, older Canadians had significantly higher blood lead levels than younger Canadians, and there has been a significant reduction in blood levels over time [40].

Impacts of chronic environmental lead exposure on health outcomes identified in Part 1

Both the WHO and Health Canada reports highlight the neurological impacts of chronic exposure [9,40]. Chronic lead exposure has been shown to impact multiple systems and is associated with neurologic, renal and hematologic disorders. High levels of lead exposure have been associated with low IQ in children, and this is noted to be the most consistent finding among children [9]. This association was also recently reported in the well-characterized, prospective, longitudinal

Dunedin cohort, where childhood lead exposure was associated with declining IQ, and decreasing socioeconomic status, after adjusting for confounds [42].

Dementia

Epidemiologic studies implicate lead in cognitive deficits including memory loss, impaired reaction time, and impaired verbal concept formation [40]. Exposure to environmental lead is associated with cognitive decline in older adults, and the relationship appears to be causal [43]. Lead has been proposed as an etiologic agent in Alzheimer's dementia, the most common form of dementia, [44] and the possible nature of the connection has recently been reviewed [45]. In support of the relationship between lead and the development of dementia, lead exposure has been associated with Alzheimer-related pathological changes in animal studies [40].

Suicide, homicide, and crime

Suicide, homicide and crime were not specifically mentioned in the WHO or Health Canada reports on the impacts of environmental lead [9,40].

Whether lead exposure is associated with an increased risk of suicide was directly tested in a large cohort study of 81,067 lead-exposed workers in South Korea. The cohort was divided based on blood lead levels into a high- and low-lead groups ($> 20\,\mu g/dl$ and $< 10\,\mu g/dl$, respectively), and analyses were adjusted for age and exposure to other metals. The causes of death were compared between the groups. All-cause mortality was higher in the high-lead group for both sexes. The high-lead group had significantly higher risk of suicide in men. Given the low incidence of suicide, there were only 13 deaths in the male population, nonetheless a significant association with lead was identified [46].

Environmental lead exposure through air pollution has been associated with increased rates of homicide in the United States after accounting for other environmental pollutants and sociodemographic factors [47].

As part of an ongoing project to measure blood lead levels in St. Louis City, Missouri, a recent ecological study assessed the relationship between areas where high blood lead levels are found and rates of violent crimes, on the basis that lead exposure risk is concentrated geographically [48]. The authors used blood lead level data from 59,645 children. This indirect study found that homicide and violent crimes were significantly associated with areas with higher blood lead levels.

Non-psychiatric medical effects

In a prospective study of 14,289 adults from the National Health and Nutrition Examination Survey (NHANES-III), Lanphear et al. [49] correlated blood lead level with cardiovascular outcomes over a mean follow up of 19.3 years. Despite generally low blood levels and only a single measurement, the authors identified large and statistically-significant associations with mortality, reporting population attributable fractions of blood lead to be 18.0% for all-cause mortality, 28.7% for cardiovascular disease mortality, and 37.4% for ischemic heart disease mortality [49].

Part 3: Link between lithium and lead

Epidemiologic and cross-sectional human studies

Very few studies identified examined both lithium and lead on health outcomes in humans. On the basis of the systematic review from Part 1, no abstract reviewed indicated drinking water lithium and health outcomes included a measure of lead. A study investigating the impact of trace elements on ischemic stroke found higher serum lithium and lead in stroke patients compared to healthy controls and did not test for interaction [50]. A Turkish study investigated the impact of lithium and lead in drinking water on body composition and found very low levels of both in the water supplies and no significant association with either [51].

Animal studies

On the basis of two translated abstracts, a group from China reported that administering lithium to rats mitigated lead-induced hippocampal damage and memory impairment, [52] and neuronal damage [53].

Wang et al. sought to test whether pre-treatment with lithium can mitigate the toxic effects of lead on the liver, spleen, kidney, and brain, and performed a number of experiments in vitro and with mice [54]. The main mouse experiment compared four groups, with each group receiving different daily injections over 2 weeks: saline (control), lead, lithium, and a group with injection of lithium then lead 2 h later. On gross and microscopic examination, they found that lithium pre-treatment significantly mitigated the damage to the spleen, liver and kidney seen in the lead-only group. The lead-only group performed significantly worse on a memory test than the l-pretreated group, which performed nearly as well as controls.

In an experiment to determine the effects of lead, lithium and the combination on thyroid function in rats, Singh and Dhawan found that, compared to controls, lead treatment increased thyroid ^{131}Iodine uptake, lithium treatment decreased ^{131}Iodine uptake, and the combination of lithium and lead caused the largest increase in ^{131}Iodine uptake [55], demonstrating that lithium and lead have the potential to interact.

Another rat experiment showed that lithium and lead both alter the uptake of other trace ions in rats, including an interaction between lithium and lead with respect to arsenic uptake: lead increased arsenic uptake significantly; lithium alone did not affect arsenic uptake, but in combination, lithium mitigated the uptake of arsenic [56].

In-vitro studies

Banijamali and colleagues sought to test whether lithium could mitigate the toxic effects of lead on non-adherent mouse bone marrow stem cells, a known target of lead toxicity. They found that lithium administration significantly reduced cell apoptosis and necrosis induced by lead [57].

Part 4: Biological mechanisms

Recent reviews synthesize the vast research into the respective physiological impacts of lead and lithium [8,58]. The mechanisms of each are broad and an exhaustive review is beyond the scope of this report, but the processes are affected by both elements and can be highlighted.

GSK-3 is implicated in the pathophysiology of dementia and involved in phosphorylation of tau, a hallmark neurolopathological feature of Alzheimer's dementia. An experimental study in rats showed that perinatal lead exposure stimulated GSK-3, increasing GSK-3 dependent tau hyperphosphorylation [61]. Conversely, lithium inhibits GSK-3 activity [8]. In the study by Wang et al. described above, pretreatment with lithium mitigated lead-associated reduction of phosphorylated-GSK-3β [54].

An additional mechanism that appears to be oppositely affected by lithium and lead is Na^+/K^+ ATPase. Lithium increases Na^+/K^+ ATPase while lead inhibits it [8,58]. Lithium inhibits the calmodulin-related activities of adenylate cyclase and protein kinase A, while lead activates protein kinase C and induces calmodulin-dependent processes [8,58]. Both lithium and lead affect *N*-methyl-d-aspartate (NMDA) receptors, influencing calcium and other ion transport in the brain.

Calcium homeostasis across the blood-brain barrier is tightly regulated, with calcium adenosine triphosphatase (ATPase) being the main transporter. Lithium may reduce the activity of this transporter [59]. Additionally, lithium stabilizes intracellular calcium via NMDA receptor antagonism and inhibition of inositol monophosphatase [60]. By comparison, lead crosses the blood-brain barrier by substituting for

calcium, both being divalent cations.

Discussion

Lithium in drinking water (Part 1)

The systematic review in Part 1 is the most extensive and most recent conducted to date and is a major strength of this report. This review highlights the growing evidence base supporting a beneficial association of water-supply lithium with various outcomes.

While some studies included covariates of possible confounds, many did not, which is a limitation of this review. However, this elevates the importance of looking at the consistency of the association across different countries, as certain geographic confounds (e.g. a city high in poverty by chance also having low levels of drinking water lithium) may account for a spurious association in one study, but not in all, and can therefore be accounted for in a systematic review. The most concerning potential confounds are those where lithium levels are systematically associated with psychiatric risk factors, but not in a biological sense. For example, one study used altitude as a covariate and found that the association between suicide and lithium depended on altitude, but no other study included this as a covariate. A meta-analysis, which would quantitatively combine the different studies, may add further value, and may be feasible given the common reporting of lithium levels and suicide incidence ratios.

The evidence is strongest for suicide, where higher drinking water lithium has been associated with lower suicide rates across different continents and time periods in the majority of studies. Fewer studies address the relationship with homicide, crime, but there is support for this relationship as well. Two studies address dementia, with the recent study by Kessing notable for its large sample size and robustness of measurements of both lithium and clinical variables, suggesting a negative correlation between drinking water lithium and dementia in Denmark. The findings would have been strengthened if the authors had controlled for potential demographic, social and geographical confounding variables.

On the whole, the epidemiologic studies support the negative association between drinking water lithium and a reduction in psychiatric outcomes, most strongly for suicide and dementia. The non-psychiatric medical effects are less studied, with only one investigating all-cause mortality and another for ischemic heart disease; though both were positive studies. Future studies are warranted and should include social and geophysical covariates, especially those that may vary with lithium in geographically distinct regions, such as altitude. An additional covariate that has not been considered could be the major sources of food supply, as food is also a source of lithium, and if the food is not made locally, then it may reflect lithium levels where it is grown.

Environmental lead exposure (Part 2)

Unlike in Part 1, the review of the effects of lead exposure did not include an inclusive systematic search of the primary literature and is a limitation of this report. However, compared to drinking-water lithium, the effects of environmental lead are generally better studied and reviewed, given the known public health concerns.

Unlike with lithium, where water is a main source of exposure, and where levels are measurable and consistent within a large area served by a single water supply, estimating lead exposure is more complicated. Lead exposure by water is more associated with local plumbing. Additional routes of exposure are also more varied within an area, and more challenging to measure, such as air (e.g. proximity to a roadway), soil, and dust (e.g. from lead paint). Despite lead accumulating in the body, measures that reflect long half-life are invasive or costly (bone measurement by biopsy or X-ray fluorescence) as compared to serum tests. Therefore, population studies of lead are challenging and more susceptible to ascertainment bias.

Lead is present in the environment, though levels in general are declining. Nonetheless, current generations have been exposed to its effects and there is sufficient evidence to conclude that lead could have affected individuals where a beneficial effect of lithium was noted. Likewise, since the pioneering work of Needleman [62], the general neurotoxicity of chronic lead exposure has been well established, especially in children, where the relationship with IQ has been replicated in multiple longitudinal studies. Recent reviews combining longitudinal, cross-sectional and animal studies suggest that lead is associated with cognitive impairment and specifically dementia in late life. Interestingly, a decline in the incidence of dementia over time has been noted [63], but it does not appear that the role of lead (which is declining simultaneously) has been proposed or tested as a factor, a separate hypothesis that warrants further study.

The link between lithium and lead (Part 3)

The paucity of epidemiological studies that measure both lithium and lead is a major limitation. This question has not been investigated adequately. A future study could include measures of environmental lithium and environmental lead levels. We therefore turned to studies that separately investigated the associated health effects of environmental lithium and lead to see whether each element had opposing, complementary associated health effects.

On the basis of our review, drinking water lithium may be *negatively correlated* with rates of suicide, homicide, dementia, general psychiatric and behavioural concerns, all-cause mortality and ischemic heart disease, with evidence of varying quality. In contrast, there is no evidence supporting a protective association of drinking water lithium on bipolar disorder, with one large negative study. Environmental lead exposure appears to be *positively correlated* with suicide (in men), homicide, cognitive impairment and dementia, lower IQ, lower socioeconomic status, all-cause mortality, cardiovascular and ischemic heart disease, with evidence of varying quality. Therefore, environmental lithium and lead exposure appear to have complementary associated health effects, supporting our hypothesis.

A lack of experimental studies in humans to test the possibility that lithium mitigates lead is an unsurprising but significant limitation. However, animal studies support a protective role of lithium in lead toxicity. The study by Wang et al. strongly supports the role of lithium in preventing lead-induced toxicity including impacts on brain and behaviour [54]. This important study warrants replication. Future animal studies could test whether very low doses of lithium also have a protective effect on cognition and neuropathology in chronic lead exposure.

In vivo studies in humans could theoretically be used to clarify the role of lithium in protecting from lead-related toxicity. For example, there are large databases of participants who have undergone structural magnetic resonance imaging, cerebrospinal fluid analyses and positron emission tomography to quantify the amount of amyloid, an Alzheimer's-related neuropathological finding. It would be possible, with considerable cost and effort, to obtain biomarkers of lead exposure from bone, in addition to estimating lithium exposure based on place of residence. This would enable testing to see whether lead correlates with Alzheimer's related neuropathology, and whether environmental lithium was negatively correlated with neuropathology. A first step may be to establish a relationship between bone lead accumulation and Alzheimer's pathological changes in vivo.

Biological plausibility (Part 4)

There is significant overlap in the pathophysiology of lead toxicity and the pharmacodynamics of lithium. While this is circumstantial evidence and does not imply that lithium protects against the lead toxicity, an absence of overlap would have challenged the hypothesis that lithium and lead interact. These data are correlational, and it is a

challenge to ascertain whether observed phenomena are direct or downstream effects of lithium and lead. However, these possibly overlapping mechanisms may also provide a place to look in future animal studies as mentioned above, for example, in comparing groups exposed to lead, lithium and both, to assess group differences in GSK-3, intracellular calcium, NMDA receptor binding, and Na^+/K^+ ATPase activity.

Conclusions and consquences of hypothesis

This report sought to review several disparate bodies of evidence to answer several questions to clarify whether the environmental exposure to lithium may mitigate the harms of chronic environmental lead exposure. It does not appear that this question has been asked before, but despite the novelty of the question, there is significant circumstantial evidence supporting the hypothesis.

On the basis of this review, environmental exposure to low levels of lithium is negatively associated with suicide, homicide, and possibly with dementia, criminality, other psychiatric disturbances, ischemic heart disease and all-cause mortality. In contrast, low levels lead exposure is positively correlated with similar outcomes. Lead is present in the areas where lithium has been associated with better outcomes. Additional evidence supporting the possibility that lithium reduces the neurotoxic effects of lead comes from animal studies. There is significant overlap in the neurophysiologic mechanisms affected by lithium and lead, especially as they both impact calcium signalling pathways and GSK-3. Further studies are required to clarify each of these areas, but the current literature is consistent with the hypothesis. Ultimately, a randomized controlled trial using chronic low dose lithium would be required to confirm a causal relationship in humans. However, our hypothesis is well-supported by the current literature.

On the other hand, there may also be multiple mechanisms at play: the mitigation of lead toxicity might explain part of the benefit of lithium in some individuals. An observation that could call the lead hypothesis into question is the overlap in the benefits of lithium observed at clinical doses and microdoses found in drinking water (i.e. reduction in suicide, prevention of cognitive decline). This may suggest a common mechanism between clinically dosed and microdose lithium exposure. The notable exception is that microdose lithium has not been identified to be associated with a lower risk of bipolar disorder. Therefore, the partial overlap in lithium's clinical effects with the associated outcomes of drinking water lithium could merely reflect confirmation bias across the literature. Recent research into correlates of drinking-water lithium is likely in large part motivated by the known clinical benefits of lithium, with the most recent studies investigating suicide, bipolar disorder, and dementia. There may therefore be systematic or confirmation bias reflected in the available literature. It is notable that there is no evidence to support a benefit of drinking water lithium on bipolar disorder. That is, the effects associated with drinking water lithium appear to map better to the opposite effects of lead exposure than they do to the effects of lithium at clinical doses.

While it is currently premature for this hypothesis to have clinical consequences, there is currently sufficient evidence to support the consideration of lead exposure in epidemiologic studies investigating the impact of drinking water lithium. In these future studies, outcome measures should include the effects of chronic lead exposure. Given the potential public health implications, these are important studies to be done.

Some investigators have concluded that lithium is an essential nutrient on the basis of the observed benefits, including the purported psychiatric benefits reviewed here [5]. This may be premature without a mechanistic understanding or robust evidence from a randomized controlled trial and without safety trials. For example, if this report's hypothesis is true, the majority of the benefit of lithium may be seen in those exposed to the highest levels of lead. A small benefit observed across the general population may be a watered-down average, where a small subset of the population has a much greater effect (e.g. those with specific mental disorders, genetic vulnerabilities, and/or specific environmental exposure such as to lead). Further, even if lithium is beneficial on average, as with any treatment, the possibility of harm must be considered, and adds to the importance of identifying the subgroups who stand to benefit. Given the dramatically smaller dose range as compared to current clinical practice that may be beneficial in reducing lead toxicity, the safety profile including therapeutic window would be favourable, and the blood level monitoring that is required in current clinical practice would likely not be required, but this would have to be confirmed in safety trials.

Additionally, if the hypothesis of this report is proven to be true, microdose lithium may one day be considered in areas where environmental lead remains high, and where reduction of lead contamination has failed or is infeasible. If the benefit of microdose lithium can established in reducing lead toxicity in humans, microdose lithium supplementation or even addition of lithium to the water supply may have benefit, analogous to fluoride for tooth decay. Another area of investigation may be the possible role of microdose lithium in localized lead contaminations as in the Flint water crisis, analogous to the use of potassium iodide after exposure to radioactivity. With further investigation into these areas, microdose lithium may be confirmed to have significant public health benefits.

Conflicts of interest

None.

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Ethics statement

We did not conduct experiments on humans or animals for the purpose of this manuscript, and therefore no review board was required.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.mehy.2018.04.005.

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