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International Journal of Bipolar Disorders (2024) 12:32
https://doi.org/10.1186/s40345-024-00348-5

International Journal of Bipolar Disorders

REVIEW

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Trace lithium levels in drinking water and risk of dementia: a systematic review

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Abstract

Background Since its debut in 1949, lithium (Li) has been regarded as a gold standard therapy for mood stabilization. Neuroprotective effects of Li have been replicated across many different paradigms ranging from tissue cultures to human studies. This has generated interest in potentially repurposing this drug. However, the optimal dosage required for neuroprotective effects remains unclear and may be different than the doses needed for treatment of bipolar disorders. Recent studies on trace-Li levels in the water suggest that Li, could slow cognitive decline and prevent dementia with long-term use even at very low doses. The current review aims to synthesize the data on the topic and challenge the conventional high-dose paradigm.

Results We systematically reviewed five available studies, which reported associations between trace-Li in water and incidence or mortality from dementia. Association between trace-Li levels and a lower risk or mortality from dementia were observed at concentrations of Li in drinking water as low as 0.002 mg/L and 0.056 mg/L. Meanwhile, levels below 0.002 mg/L did not elicit this effect. Although three of the five studies found dementia protective properties of Li in both sexes, a single study including lower Li levels (0.002 mg/l) found such association only in women.

Conclusion The reviewed evidence shows that trace-Li levels in the water are sufficient to lower the incidence or mortality from dementia. Considering the lack of options for the prevention or treatment of dementia, we should not ignore these findings. Future trials of Li should focus on long term use of low or even micro doses of Li in the prevention or treatment of dementia.

Keywords Neuroprotection, Lithium, Dementia, Micro dosing

Introduction

Lithium was introduced to psychiatry in 1949 (Cade 1949). Since then, it has reached and maintained a position as the gold standard for the treatment of mood disorders. Even after 75 years of use, Li is still surprising researchers with new pharmacodynamic effects, which open the door to potential new indications. For example, pre-clinical research shows that lithium (Li) can protect neurons from a wide range of toxins and neurodegenerative disease models (Lauterbach and Mendez 2011; Qu et al. 2011; Dou et al. 2005; Nunes et al. 2015). There is evidence from brain imaging studies in human participants suggesting neuroprotective effects of Li in cross-sectional, longitudinal studies and even randomized controlled trials (Lyoo et al. 2010). In consequence, Li could be considered for the treatment of neurodegenerative disorders.

Despite the extensive pre-clinical and brain imaging evidence, clinical trials on the neuroprotective effects of Li remain sparse. This is presumably related to concerns regarding the toxic effects of Li (Mecê et al. 2022), which are dose dependent and may be particularly pronounced

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among the elderly population (Arnaoudova 2014; Adityanjee and Thampy 2005). These concerns are perhaps exaggerated as there is controlled evidence that Li can be safely used even in cognitively impaired elderly (Aprahamian et al. 2014) and Li-treated elderly individuals even show superior general and mental health outcomes than their BD counterparts who are not treated with Li (Forlenza et al. 2022). More importantly, the Li doses needed for neuroprotective effects may differ from those used to treat mood disorders.

There is evidence that subclinical or even micro-dose levels may suffice to slow down the progression of cognitive impairment (Andrade Nunes et al. 2013; Forlenza et al. 2011). A randomized, placebo-controlled study conducted in Brazil investigating micro-dosing of Li (300 μg), observed a slowing of cognitive decline following a 10-week treatment course in people with AD (Andrade Nunes et al. 2013). Another randomized, controlled trial of subclinical doses of Li (0.25 mmol/L–0.5 mmol/L) found a significant decline in P-tau accumulation in the cerebrospinal fluid of individuals (Forlenza et al. 2011; Forlenza et al. 2019), as well as a positive impact on preserving functional capacities. Consequently, Nano Lithium has been featured prominently in the list of repurposed drugs for neurodegenerative disorders (Cummings et al. 2023). These findings suggest that even doses that are much lower than those used for the treatment of mood disorders may be effective in preventing cognitive decline. These studies hold promising implications for the potential of Li as a viable treatment for dementia.

There is now a growing body of evidence that even trace levels of Li, such as those found in drinking water may reduce the risk of dementia over a lifetime of exposure (Duthie et al. 2023; Fajardo et al. 2017; Muronaga et al. 2022; Kessing et al. 2017; Parker et al. 2018). These studies, however, have not been concisely reviewed, which is the primary aim of the present manuscript. Reviewing this topic would establish evidence base, which could support future trials of low dose Li to prevent or delay the onset of dementia.

Methods

Search strategy

The initial search for the present review was conducted on May 12th, 2024. The terms used to gather the studies from PubMed for this review included: (Lithium) AND (Drinking Water) AND (Dementia) AND (Humans). This primary search yielded 13 studies which were saved and subsequently uploaded into Covidence, a systematic review tool for abstract screening. Two screeners were involved in this procedure to ensure the studies included were appropriate for the present review (JFP, TH).

Eligibility criteria

The exclusion and inclusion criteria for this review were determined a priori using the "eligibility criteria" tab in Covidence. These eligibility criteria were pre-established to increase the consistency and reliability of the identified sample, while potentially controlling for bias.

Inclusion criteria

The inclusionary criteria for the population included studies on human adults (18 +) focusing on dementia outcomes in relation to trace or low-Li levels in drinking water. Finally, only papers published in the English language were considered in this review.

Screening process

13 studies were uploaded into Covidence for screening. Upon reviewing the 13 abstracts, 3 studies were deemed irrelevant. Two of those studies were excluded as their target population did not meet the a priori-determined eligibility criteria (one focusing on mice and another on adolescents) and one due to being altogether unrelated to the topic of review.

The 10 studies that remained underwent an in-depth full-text review, in which 6 were excluded—1 consisted of a brief article (1-page), while 3 fell under the criteria of 'comment & response' to one of the original reports, and 1 study was excluded for being a systematic review. Lastly, an additional study was excluded as they did not focus on dementia but rather on psychotic experiences (Shimodera et al. 2018).

After a comprehensive review, 4 of the 13 initial studies remained. These 4 studies in addition to the one included upon reviewing the literature, were then used for the data extraction procedure (Fig. 1).

Data extraction

5 studies were included in the data extraction process, aiming to summarize the results and methodological strengths and limitations.

Data items

Data extraction consisted of retrieving the following: (1) The country in which the study was conducted; (2) Methods of recruitment and population sampling; (3) Measurements of Lithium levels; (4) Outcomes; and (5) Covariates.

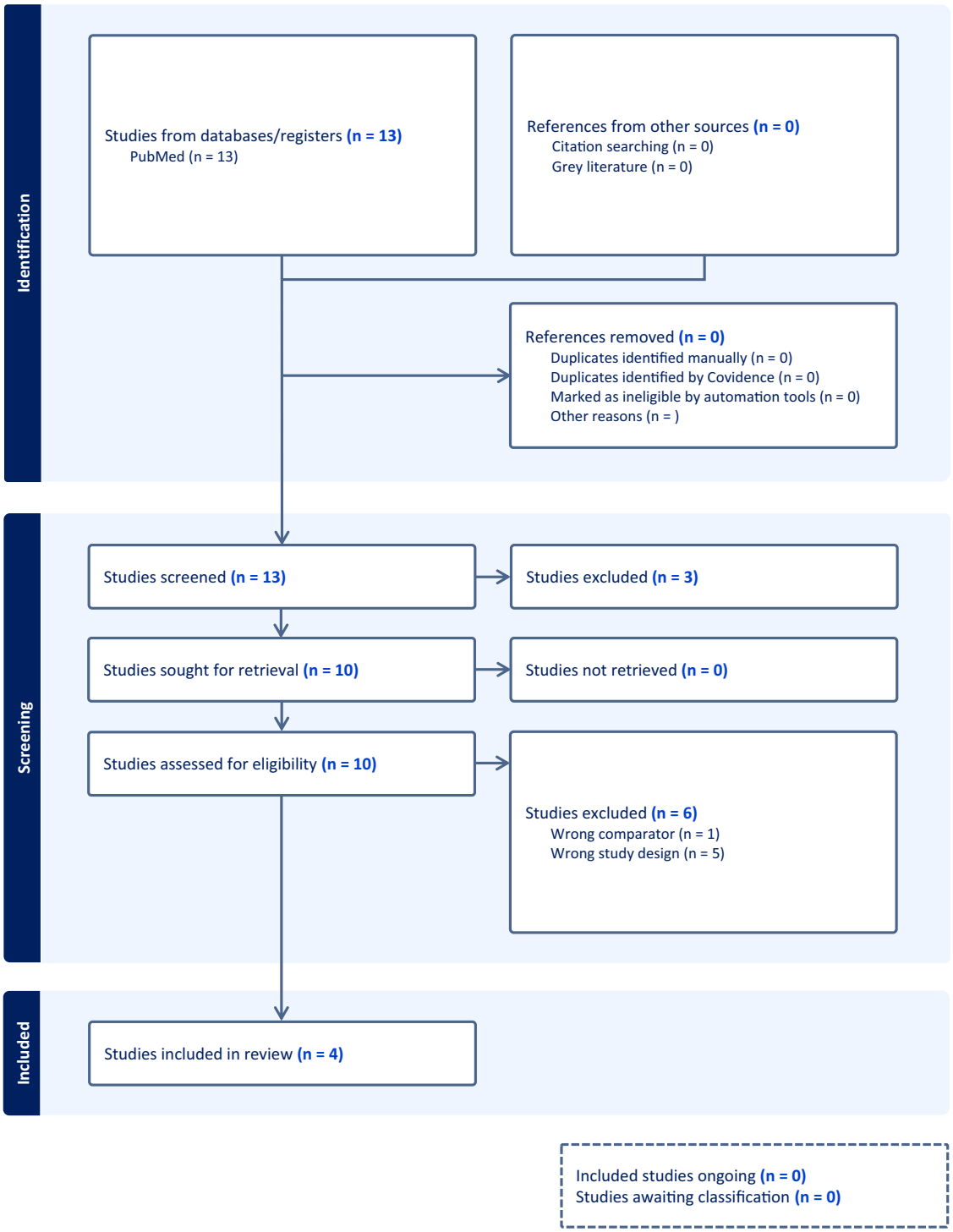

Fig. 1 Covidence PRISMA flowchart

Results

Study Descriptions

Study 1 Low-level lithium in drinking water and subsequent risk of dementia: A cohort study (Duthie et al. 2023).

This study was conducted in Scotland pooling from the general population by using the Scottish Mental Survey 1932 (MS1932), which included almost all school-aged children from June 1932. Most of these children had been born in 1921. Despite efforts to include all children, the study did exclude about 5.6% of them for failure to complete the survey. Later in life, 43% of these individuals were identified using medical and primary care records, as well as location.

Measurements of Li were collected from the "Scottish Water" database sampled in 2014. 285 Li samples were collected, and the remaining were gathered by using "idw ()" in R to interpolate values using inverse distance weighting. These values were then assigned to individuals based on their geographical location. Gathered standardized Li concentration levels were broken down into 5 quantiles.

The main outcome measured by the study was the risk of dementia. The authors controlled for the participants' IQ at age 11 and their sex. The study, however, did not consider dietary sources of Li, Li content in bottled water, access to health care, age of diagnosis or changes of address.

Study 2 Examining the Relationship between Trace Lithium in Drinking Water and the Rising Rates of Age-Adjusted Alzheimer's Disease Mortality in Texas (Fajardo et al. 2017).

This study was conducted in all Texas counties. Data was gathered using the "Wonder's Compressed Mortality Database". Encompassing changes in mortality rates between years 2000–2006 and 2009–2015.

Li cationic levels were collected from the public water supply using the "Texas Water Development Board Groundwater Database". This information was obtained from the database using the filters "quality" and "last 10 years". Overall yielding 6180 water samples across 234 counties in Texas.

This study aimed to investigate the Li levels and Alzheimer's mortality rates. To further inquire about this relationship, data on race, gender, and rural residence, were obtained from the Census Bureau's Population Estimation Program; air pollution data from the CDC Wonder Environmental Database; and physical activity, obesity, and type 2 diabetes (T2D) from the National Diabetes Surveillance System. This study did not account for time individuals may have spent in other areas outside Texas or the length of Li exposure,.

Study 3 Lithium in drinking water and Alzheimer's dementia: Epidemiological Findings from National Data Base of Japan (Muronaga et al. 2022).

This research was conducted in Japan, including 808 regions, containing 785 cities and 23 wards of Tokyo. 91% of the population living in these areas were included in the study. Information on AD individuals was compiled from anonymous AD claims to the Nippon Telegraph and Telephone (NTT) survey, the Ministry of Health, Labor, and Welfare of Japan database, and 2 major medical insurances (one for the early elderly and another for the later elderly). Despite including the 2 primary insurance companies in Japan, the research team was unable to find all anonymous claims, limiting their sample.

Lithium measurements came from 988 water samples congregated from the main rail station or municipal office between 2010 and 2015. A 3rd party used mass spectroscopy to analyze the levels of Li.

To investigate the prevalence of AD, researchers collected Li levels in water and AD incidence rates. 4 variables from the Statistics Bureau Ministry of Internal Affairs and Communications database were considered, including (1) the proportion of one-person households; (2) the proportion of people in primary industry employment; (3) the annual total sunshine hours between 2010 and 2015; and (4) the number of beds in psychiatric hospitals between the same period. The present study also failed to consider dietary sources of Li, use of NSAIDs, the difference of Li in mineral water in Japan when compared to other locations, gender, education, race, and metabolic factors (i.e. obesity, T2D) or changes of adress.

Study 4 Association of Lithium in Drinking Water with the Incidence of Dementia (Kessing et al. 2017).

This Danish population-based study pooled data from the population registry for individuals with dementia by obtaining information on Danish individuals from national reports (Statistics Denmark, the Danish National Patient Register—DNPR, and the Danish Register of Causes of Death—DPCRR) from 1986 to 2013. Control individuals were randomly assigned, and sex/age matched those of the dementia group. Individuals who lacked information on the municipality of residence between 1986 and the index were excluded from the study.

151 samples of the public water reservoirs were gathered between 2009–2010 and 2013. The researchers used these samples to estimate Li in water using the Kringing interpolation methods. This method accounted for individuals moving to different areas in Denmark during the time being analyzed.

To investigate the incidence of dementia and its relationship to Li exposure via drinking water, gathered demographic data from the population. The study did not

adjust for accessibility to health care (as it was deemed similar across the board) and other environmental factors such as urbanicity.

Study 5 Association between groundwater lithium and the diagnosis of bipolar disorder and dementia in the United States (Parker et al. 2018).

An investigation on the association between groundwater Li and diagnosis of BD and dementia was conducted across the United States. Individuals' inpatient hospital and long-term care data were gathered using the Truven Health Marketscan Commercial Claims & Encounters (2003–2010), Medicare recipients, and Medicaid Analytic eXtract (2011–2012). This generates potential for selection, and it was not exhaustive of the sampling population.

Lithium levels were obtained from the US Geological Survey from 3000 + drinking water wells from 1992 to 2003. The overlap between this sampling and the study population is not clear. To investigate the impacts of groundwater Li and dementia diagnosis, demographic data was collected from the Health Resources & Services Administration (HRSA) and the 2010 Area Health Resources Files (AHRF). The study considered median age, education, race, ethnicity, and the number of beds in primary care per 1000/individuals.

The study did not explain in detail the use of covariates on the association of dementia onset and Li levels in groundwater. This study was the least comprehensive and had the greatest potential for bias.

Association between Li levels and dementia

The sample size varied in the studies from 37,597 to 35 000 000. Lithium levels ranged from 0.002 to 0.027 (mg/L). The rates of dementia varied widely; in 3 studies the rates were between 5.8% and 9.6%, while in 1 study the rates were very low at 0.041% (See Table 1), likely reflecting marked selection bias.

Table 1 Lithium levels and dementia rates

Study	Mean lithium levels (mg/L)	Population size	Dementia rates in their sample(%)
Parker et al. 2018)	0.027	4227556	0.041
Muronaga et al. 2022)	0.002	35000000	5.8
Kessing et al. 2017)	0.012	807384	9.13
Duthie et al. 2023)	0.001	37597	9.6

This table does not include Fajarado et al., (Fajardo et al. 2017), as this study considered mortality from dementia instead of incidence. The average Li levels in this study were 0.056 mg/l

4 of the 5 studies found a significant association between Li levels and lower risk of dementia or lower dementia mortality rates, when they did not control for any confounders. One study did not find any association between Li and dementia and reported one of the lowest Li levels (Duthie et al. 2023).

After controlling for available confounders, one found an association between Li levels and lower risk of dementia in both male and females (Kessing et al. 2017) and one study in females only (Muronaga et al. 2022). In contrast, the association between lithium and dementia disappeared when controlling for county demographics and healthcare resources (Parker et al. 2018), and physical inactivity, obesity and T2D (Fajardo et al. 2017). While all studies controlled for sex, the additional confounding factor varied between studies and surprisingly, age categories were not controlled in any of the studies.

The association between trace levels of Li and dementia outcomes was non-linear in at least one of the studies (Kessing et al. 2017).

Discussion

Most of the studies found an association between trace-Li levels and dementia, even though this association disappeared after controlling for confounders in some studies. It is surprising that three studies showed association between risk of dementia and lithium levels that were orders of magnitude lower than the levels used in clinical practice, i.e. as low as 0.002 mg/L (Muronaga et al. 2022; Kessing et al. 2017; Parker et al. 2018). Dose–response relationships between trace Li levels and dementia outcomes may not be linear and may not extend to very low levels (i.e. below 0.002 mg/L (Duthie et al. 2023)). Trace Li was associated with a lower prevalence of dementia as well as lower mortality from it. These findings were replicated in 4 studies on 3 continents, even despite differences between the respective countries in potential confounds. In two studies, the associations between trace levels of Li and lower incidence/mortality from dementia disappeared when controlling for a range of confounders (Parker et al. 2018, Fajardo et al. 2017), however, this was not the case in the most comprehensive, least biased study (Kessing et al. 2017).

The review points to some underappreciated mechanisms by which lithium can impact the rates of dementia, such as obesity. In the US, over 40% of the adult population is obese (State of Obesity 2023), which is significantly higher than when compared to Denmark (OECD 2023) (18.5%) and Japan (OECD 2023) (4.5%). Interestingly, in one study the links between Li and dementia were mediated by lower rates of diabetes in those with higher Li exposure. The authors postulated possible impact of Li on insulin sensitivity. In contrast to that, the

association between Li and dementia was reported across countries which widely differed in rates of obesity and diabetes. Consequently, the effects of Li on diabetes are interesting, but may not fully account for the protective effects of Li against dementia.

The study in Japan only observed a significant relationship between Li exposure and dementia among women (Muronaga et al. 2022). In contrast, the Danish study found the effect in both men and women (Kessing et al. 2017). The range of Li values in the Danish study (mean = 11.6 mg/l) was higher than the range in the Japanese (mean = 2.39 mg/L) (Muronaga et al. 2022; Kessing et al. 2017). Females may be more sensitive to the uptake of Li (Dawkins 1995), perhaps needing lower doses to generate sufficient response.

The rationale for the use of low-dose Li is justified by better safety/tolerability and engagement of distinct molecular targets. Studies using primary neuronal cultures indicated that the effects of Li on multiple tau kinases were significantly different according to concentration range. Effects in hippocampal neurons were greater at lower concentrations (De-Paula and Forlenza 2022). Similar effects were shown on the secretion of pro- and anti-inflammatory interleukins in co-cultures of neurons and glial cells (De-Paula and Forlenza 2022). A proteomic/gene ontology study in triple-transgenic (3xTg) AD mice showed distinct effects of therapeutic and subtherapeutic concentrations of Li on homeostatic pathways mediated by the interaction between neurons and glial cells (Rocha et al. 2020). Likewise, lower dosing was also a determinant of the effect of Li on the preservation of telomeres in the presence of amyloid-beta toxicity both in primary neurons (Themoteo et al. 2022) and in 3xTg-AD mice (Cardillo et al. 2018). Nonetheless, experimental models have not examined the biological effects of Li at trace levels.

Implications

The reviewed literature has important implications for the medical field. Li benefits have been repeatedly demonstrated. This body of research is no different as it highlights the capacity of even significantly low Li levels to promote health benefits. It is striking that Li is linked with a lower risk of dementia or dementia mortality at levels that are up to one thousand times lower than those used clinically. The reasoning behind this could be that this effect is related to the lifelong duration of exposure. Environmental uptake of Li allows individuals to use Li in the very early stages of neurodegenerative processes, which would otherwise remain undetected and untreated. At these levels, Li is safe to use even among the elderly. If safety issues are not a major concern, it would be unfortunate if the lack of patentability of Li (Hajek and Young 2016) limited future research into its neuroprotective and dementia-preventing effects of Li.

In the present, treatments for prevention and improvement of the course of dementia are lacking or inefficacious. This body of work draws attention once again to Li, as a potential therapeutical intervention for neurodegenerative disorders. We need studies of the long-term use of low doses of Li especially in people who are unaffected yet, but at an increased risk of dementia, such as people with APOE4 or obese individuals or those with morbus Down. Individuals with insulin resistance or diabetes may be another group with an increased risk of dementia (Cholerton et al. 2013), where Li could be particularly helpful considering the neuroprotective and insulin-sensitizing effects of Li.

Limitations

The reviewed studies have a range of limitations, including the absence of direct measurement of healthcare (Muronaga et al. 2022; Parker et al. 2018), geographical and geological factors accounting for natural Li distribution (Fajardo et al. 2017; Muronaga et al. 2022), dietary habits and other lifestyle habits that may also impact the development of dementia. A fundamental aspect when interpreting the results are Li sampling and levels. Although the Li trace-level samples in Texas were higher in number, they were not the most comprehensive as they did not consider these levels before 2006 despite including prior years in the population sample analysis (Fajardo et al. 2017). Similarly, in the US study, groundwater Li levels, although comprehensive only included data up to 2003 (Parker et al. 2018). The studies in Scotland and Japan included overall comprehensive samples of the Li levels in water (Duthie et al. 2023; Muronaga et al. 2022). However, across the five, the study in Denmark, was notably the most thorough, which included the Kringing interpolation method, allowing the researchers to consider the time individuals spent in different parts of the country to calculate an overall lifetime exposure to Li (Kessing et al. 2017).

The Scottish study (Duthie et al. 2023) claims to have found a trend to increased risk in females at lithium levels below but not above 2.1 μg/L. Specifically, in females there was an association between lithium level and increased dementia risk compared to the lowest decile in all deciles except the highest, corresponding with lithium levels 2.1–9.19 μg/L. In their main analyses they did not find an association between Li levels and risk of dementia. We list this study as finding no association between Li and risk of dementia.

Another issue is the potential for bias in the evaluated studies. The two studies that were conducted in Europe had highly comprehensive population samples,

including national registries (Duthie et al. 2023; Kessing et al. 2017). Yet, one of them found and the other did not report associations between Li and dementia, likely due to very low Li levels. Even though the Japanese study was based on insurance claims it included 91% of the population (Muronaga et al. 2022). Study by Parker and colleagues (Parker et al. 2018), used different sources of information, such as inpatient hospital records, long-term care and therapy claim files (CCAE, Medicare, Medicaid, etc.), the sample size and the rates of dementia were much smaller than expected (low Li sample = 34/ 10 000; high Li sample = 48/10 000) or found in the other studies. The reason why this association disappeared after controlling for demographic and healthcare factors, could be due to the small sample and biased sampling resulting in very low rates of dementia. The more comprehensive, less biased studies all showed an association between trace Li and dementia.

Conclusion

In conclusion, replicated evidence suggests that environmental exposure to Li trace levels may be sufficient to lower the risk or mortality from dementia. Women may be more sensitive to these effects and require lower doses (Muronaga et al. 2022). The positive impact on reducing the rates or mortality from dementia was observed at very low concentrations of Li in drinking water (0.002–0.056 mg/l) (Fajardo et al. 2017; Muronaga et al. 2022; Kessing et al. 2017; Parker et al. 2018), whereas levels below 0.002 mg/L (Duthie et al. 2023) may be too low. This warrants future dose-finding studies and justifies studies using microdoses of Li to treat/prevent dementia, which are safe and well above the minimum trace levels suggested here.

Abbreviations

Li	Lithium
TD2	Type 2 diabetes
AD	Alzheimer's disease
NSAIDs	Non-steroidal anti-inflammatory drugs

Acknowledgements

Not applicable.

Author contributions

J.F.P and T.H. conducted the systematic review and double checked all information. All authors made substantial contributions to the conception or design of the work; drafted the work or revised it critically for important intellectual content; approved the version to be published; and agree to be accountable for all aspects of the work.

Funding

Dr. Tomas Hajek was supported by funding from the Canadian Institutes of Health Research (142255, 180449, 186254), Nova Scotia Health Research Foundation, Dalhousie Clinical Research Scholarship to T. Hajek, Brain & Behavior Research Foundation (formerly NARSAD); 2007 Young Investigator and 2015 Independent Investigator Awards to T. Hajek.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors agreed with the publication.

Competing interests

The authors declare no competing interests.

Received: 21 May 2024 Accepted: 13 July 2024
Published online: 30 August 2024

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