Low-level lithium in drinking water and subsequent risk of dementia

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Low-level lithium in drinking water and subsequent risk of dementia: Cohort study

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Abstract

Background: Lithium, a mood stabilizer, is known to exhibit neuroprotective effects in animal models and may have anti-dementia effects.

Aims: We used data from Scottish Mental Survey 1932, a population-based cohort study, to investigate the association between lithium in drinking water and dementia rate in humans.

Method: Lithium levels in drinking water from 285 sampling sites across Scotland dating from 2014 were obtained from the sole public water provider (Scottish Water). Dementia and non dementia cases were identified from cohort data by electronic health records until 2012, and linked to postcode.

Results: The mean lithium level at all sampling sites was 1.45 μg/L (SD 1.83, range 0.5–18.2) and was 1.26 (SD 0.63, range 0.55–9.19) for sites matched to participant data. Of 37,597 study members, 3605 developed dementia until June 2012. Lithium levels were positively associated with the risk of dementia in women (highest in second quartile, HR 1.17, 95%CI 1.04–1.32), but there was no relationship in men (highest in second quartile, HR 0.95, 95% CI 0.81–1.12). The pattern of association was explored further by decile, and in females there was an association between lithium level and increased dementia risk compared to the lowest decile (0.55–0.68 μg/L) in all deciles except the highest, corresponding with lithium levels 0.68–2.1 μg/L.

Conclusions: Lithium levels in drinking water are very low across Scotland which limited detection of potential effect. Our results do not support an association between extremely low levels of lithium and later dementia risk. We found a trend to increased risk in females at lithium levels below but not above 2.1 μg/L.

KEYWORDS
dementia, epidemiology, lithium

Key points

- Lithium levels in drinking water are very low across Scotland which limited detection of any potential effect.

- Our results do not support an association between extremely low levels of lithium in drinking water and later dementia risk.
- At very low lithium levels the trend for dementia risk in females was not linear.

1 | INTRODUCTION

Dementia is one of the most important public health challenges of our time. In most countries the population is ageing, and the proportion of people with dementia is rising especially in later life, with significant impact on health and social care.[1,2] Most research interest has focussed on the commonest type, Alzheimer's disease. (AD) however interventional therapeutic trials have so far produced disappointing results.[3] Repurposing of existing drugs, particularly when off-patent, is an attractive strategy to bring potential therapies to the market quickly and safely. Lithium is an effective medicine for mood disorders with reported anti-suicide effects and as a result of its purported neuroprotective effects has been suggested to prevent dementia.[4–6]

Lithium exerts multiple effects in the human brain. Postulated targets of lithium include intracellular cascades involved in inflammation, oxidative stress, membrane homoeostasis, mitochondrial dysfunction, circadian function and apoptosis. One of the key targets of lithium is the GSK-3 (Glycogen-Synthase-Kinase-3) enzyme[7] and evidence suggests that modification of GSK-3 pathways has an important role in the therapeutic benefit of mood stabilisers.[8] This intracellular enzyme is involved in numerous actions relating to cell survival and growth, as well as involvement in phosphorylated tau and beta-amyloid deposition.[6,9,10] Some small studies in people with cognitive impairment treated with lithium have demonstrated increases in serum brain-derived neurotrophic factor,[11] enhanced hippocampal neurogenesis[12] and increased markers of neuroprotection on MR Spectroscopy.[13] In 2021 a review found 13 studies investigating standard lithium dose (0.4–1.2 mmol/L) for either AD or Mild cognitive impairment.[14] This included the randomized controlled trial by Forlenza et al[15] which demonstrated good evidence for reduction of cognitive decline with lithium treatment compared to placebo after 2 years, with associated changes in AD related biomarkers.

However, the level at which lithium may exert therapeutic effects in humans is unknown and a variety of studies have investigated the effect of trace lithium in epidemiological samples.[5] Lithium is a naturally occurring element and very low levels of lithium enter drinking water naturally with significant geographical variation. The meta analysis and systematic review by Eyre-Watt et al[16] summarises 27 studies examining lithium in drinking water and neuropsychological outcomes, finding reduced suicide rates and psychiatric admissions at higher levels. The outcomes for other neuropsychiatric outcomes including dementia were unclear. Previously a large Danish study involving over 731,000 participants with dementia reported a non-linear association of drinking water lithium with dementia risk.[17] Compared to the lowest levels of lithium, a protective effect was seen at levels above 15 μg/L (incidence rate ratio 0.83, 95% CI 0.81–0.85) but a concentration of between 5 and 10 μg/L led to increased risk of dementia in the study (incidence rate ratio 1.22; 95% CI 1.19–1.25). In 2018 a study from Texas suggested a protective effect of lithium for AD risk, but only at levels above 30 μg/L.[18] Most recently Muronaga et al[19] described an association between higher water lithium level and reduced AD risk in females but not males, in a study covering 91% of the Japanese population. From this evidence base we hypothesise that long term lithium exposure might be associated with rate of dementia. We investigated the relationship between lithium levels in drinking water and dementia incidence across Scotland using an existing large population cohort.

2 | METHODS

2.1 | Study sample and dementia outcomes

We used data from the Scottish Mental Survey 1932 (SMS1932) (methods described previously).[20] In brief, this study included almost all people born in 1921 and at school in Scotland in June 1932; a total of 87,498 schoolchildren took part in this comprehensive national intelligence testing exercise at mean age 11 years. A total of 5.6% of potential participants did not take part in the test because they were absent from school. The intelligence test used was a version of the Moray House Test no. 12 (MHT) from which an IQ-type score was derived and provided with the SMS1932 dataset.[21] The MHT has a high (0.8) concurrent validity with an individually-administered Stanford Binet IQ test.

Participants in the SMS1932 have been passively followed up into later life using anonymised probabilistic record linkage to electronic health records, as described elsewhere[22] (Figure 1). Approximately 43% of the 86,250 test participants (i.e., the total of 87,498 apart from those living in the counties of Angus, Fife, and Wigtown; SMS1932 ledgers for these locations have been lost) were identified in later life. Dementia cases (all cause dementia) were identified by linkage to electronic medical records: from the general or psychiatric hospital or death certificates until the linkage date at the end of June 2012 (any mention of codes 290.0–290.4, 290.8, 290.9, 291.1, 291.2, 294.1, 294.2, 294.8, 294.9, and 331.0–331.9 for ICD-9 and codes F00-F05.1, F09, G30, and G31 for ICD-10). A further source of dementia diagnoses for a subsample of the cohort was primary care records, specifically the Greater Glasgow and Clyde Nursing Homes Medical Practice which produced 32 individuals who had dementia, 17 of whom were not identified from other sources. An individual's residential location (postcode sector) was identified from the record

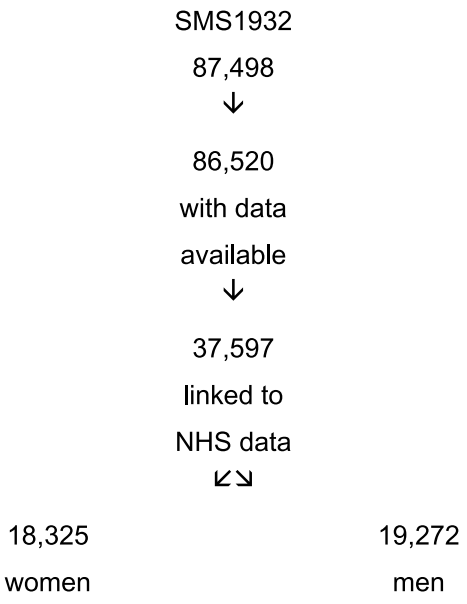

FIGURE 1 Flow chart of study participant selection.

which first mentioned dementia. For those who did not develop dementia, we recorded their residential location at the first record of hospital admission after the age of 60 years (the earliest date possible due to the beginning of electronic medical records in Scotland in 1981). For those not admitted to hospital location of death was used. This study received ethical approval from the Scotland A Research Ethics Committee (10/S1103/6).

2.2 | Environmental data

Lithium levels (μg per litre) in drinking water from one sampling period in 2014 were obtained from Scottish Water, the organization responsible for the provision and monitoring of the water supply in Scotland. Of 285 lithium sampling sites covering the whole public water supply, the site location was missing for six and these sites were excluded from our analyses. For each sampling site recipient postcodes were identified (full 6–8 character postcodes; converted to latitude and longitude based on centroid). Sampling sites were widely distributed across the country, with greater numbers where the population is more concentrated, that is, the central belt and other city areas (Figure 2). A total of 166 sites measured less than 1 μg/L (a limit of the sampling technology) and these were assigned the value of 0.5 μg/L (the mean of zero and 1 μg/L).

We used the idw() function from the gstat package for R for Windows version 3.4.3 to interpolate values for lithium using Inverse Distance Weighting across a spatial grid with spacing of 0.1 degrees of longitude or latitude. This allowed us to estimate values for areas where no measurements had been made. The mean values for each grid area were then calculated and the mean of all grid areas falling within each postcode sector were calculated (Figure 2). Values were then assigned to each individual based on their residential location.

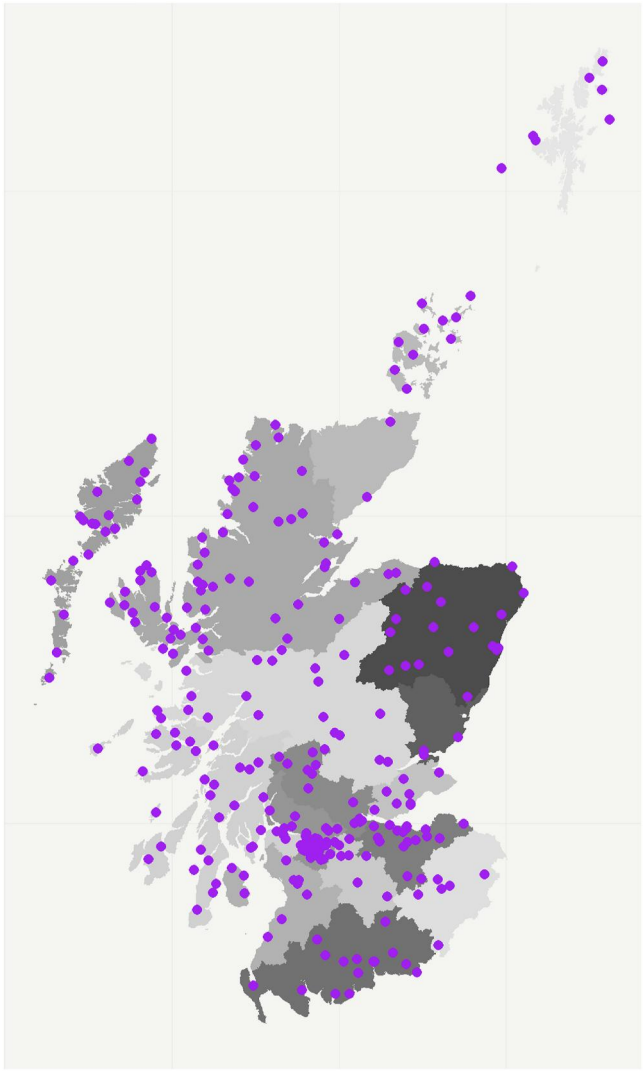

FIGURE 2 Location of lithium sampling sites in Scottish Drinking Water Quality Regulator data 2014: the Scottish Mental Survey 1932 (SMS1932) cohort.

These values were standardised and centred on zero such that a unit increase indicated one standard deviation increase in the original scale. We also calculated quartiles of lithium values to allow us to examine the shape of any association identified.

2.3 | Statistical modelling

After confirming that the proportional hazards assumption was valid using the cox. zph() function from the survival package in R (all $p > 0.1$), we constructed Cox proportional hazards models for the association between lithium levels in water with dementia death in men and women separately.[23] Age in years was the timescale and all effect estimates were additionally adjusted for age-11 IQ since this has also been linked with dementia risk in this cohort.[21] We made the decision to analyse separately by gender—despite preliminary

analyses suggesting there was no statistical interaction by sex ($p > 0.5$)—because of evidence that the pattern of geographical variation in dementia risk varies between men and women.[22] Maps were produced in R using the ggplot2 package.

3 | RESULTS

Of the whole cohort ($n = 86,250$), data for 37,597 (43.6%) individuals were available and, of these, 3605 had a record of having developed dementia at or before the linkage date in 2012. Fifty-one percent of the sample were male and all were born in 1921 resulting in an age of 93 in those still living at the time of sampling. The mean lithium level at all sampling sites was 1.45 μg/L (SD 1.83, range 0.5–18.2) and was 1.26 (SD 0.63, range 0.55–9.19) for sites matched to participant data (i.e. where participants lived) Lithium concentration in drinking water is presented in Figure 3.

Survival analyses are presented in Table 1. There was a raised hazard of dementia in all quartiles of lithium concentration compared to the lowest in women (Q2 HR 1.17, 95% CI 1.04–1.32; Q3 1.10, 0.97–1.24; Q4 1.06, 0.94–1.20) but not in men (Q2 HR 0.95, 95% CI 0.81–1.12; Q3 0.93, 0.80–1.12; Q4 0.89, 0.75–1.05). The highest quartile covered a broad range of lithium from 1.47 to 9.19 μg /L).

Given the observed pattern of association in women potentially resembling an inverted 'U' (with the highest risk in the second quartile of lithium concentration), we explored the pattern of association in more detail by dividing lithium concentrations into deciles (Supplementary item: Table S1). Numbers of dementia cases in each decile group were small, especially for men. The highest lithium decile ranged from 2.1 to 9.19 μg/L. In men, there was a raised hazard ratio in the second decile corresponding to lithium levels of 0.68–0.79 μg/L. compared to the lowest (D2 1.31, 1.01–1.50; D3 1.22, 0.94–1.58) but not in the deciles of higher concentration. In females, there was an association between lithium level and increased dementia risk compared to the lowest decile (0.55–0.68 μg/L) in all deciles except the highest decile, corresponding with lithium levels of between 0.68 and 2.1 μg/L. The increase in dementia risk was highest in the ninth decile (1.55–2.1 μg/L; HR 1.42, CI 1.16–1.73 though the relationship across deciles was not clearly linear.

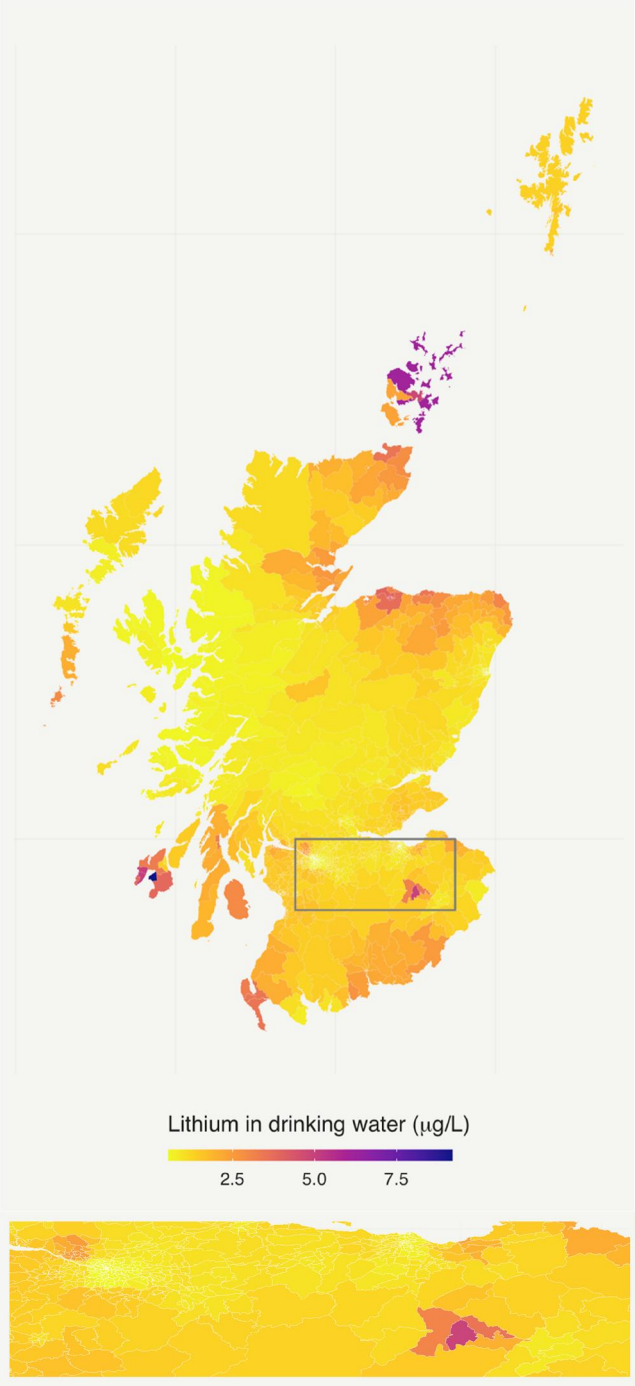

FIGURE 3 Map indicating levels of lithium in drinking water in Scotland: the Scottish Mental Survey 1932 (SMS1932) cohort. Lower panel shows an enlarged view of the Central Belt of Scotland including Glasgow and Edinburgh.

4 | DISCUSSION

4.1 | Key findings

Our main finding was no association between lithium in water supplies and dementia risk in men; however, counter to our hypothesis, in women, levels were in fact related to elevated risk. The *p*-value for the lithium:sex interaction in a Cox model was non-significant (0.373).

4.2 | Comparison with other literature

This finding is in common with work from Denmark[17] and Texas[18] which did not identify a protective effect below 15 or 30 μg/L respectively. Our present study is the first to describe the relationship between lithium concentration in the water supply and risk of

TABLE 1 IQ-adjusted hazard ratios and accompanying 95% confidence intervals for the association between mean lithium levels in drinking water and dementia occurrence in men and women: the Scottish Mental Survey 1932 cohort.

	Women				Men			
	N	Dementia *N*	HR[a] (95% CI)	P_{trend}	*N*	Dementia *N*	HR[a] (95% CI)	P_{trend}
Mean lithium levels μg/L								
Quartile 1 (low) 0.55–0.87	3532	498	1 (ref.)		3452	285	1 (ref.)	
Q2 0.87–1.09	3503	552	1.17 (1.04, 1.32)		3549	306	0.95 (0.81, 1.12)	
Q3 1.09–1.47	3449	511	1.10 (0.97, 1.24)		3584	314	0.93 (0.80, 1.12)	
Q4 1.47–9.19	3540	527	1.06 (0.94, 1.20)		3475	281	0.89 (0.75, 1.05)	
Per SD increase	14,024	2088	1.00 (0.96, 1.04)	0.92	14,060	1186	0.97 (0.91, 1.03)	0.33

Note: N.B. Sites measuring levels <1 μg/L were arbitrarily set at 0.5.

[a]Hazard ratio adjusted for age 11 mental ability.

dementia in Scotland. In Scotland the water supply is managed by a sole operator, Scottish Water, which is owned by the Scottish Government. Accordingly we are able to report on widespread sampling points which cover the whole population. Participants were of a narrow age range, thus minimising cohort effects and comprised a nationally representative sample.

Our data showed an association between lithium levels and dementia risk in females only, with increased risk at concentrations between 0.87 and 1.09 μg/L when compared with the lowest decile. Analysed further by decile, the increase in Dementia risk was highest for females between levels of 1.55–2.1 μg/L. Interestingly Kessing et al[17] in a Danish population study of over 800,000 individuals also described a non linear relationship, finding an increased risk for individuals exposed to lower levels between 0.5 and 10 μg/L compared to those below 2 μg/L. The reasons for this are unknown and may be spurious. One further possibility is that the mechanisms of action of lithium may differ with increasing dosage. This point is an important one to clarify in advance of potential public health initiatives to supplement water supplies with Lithium.

4.3 | Limitations

The 285 lithium measurements in our analysis were widespread across the country supplying 97% of the whole population and were all collected in 2014, subsequent to our dementia data linkage in 2012. In order to be certain of stability of lithium in drinking water in Scotland over time, repeated measurements from our sampling points over a number of years would be required. Scottish Water and BGS have confirmed that this data is not available since lithium in drinking water is not measured routinely in the UK or Scotland (further information available from authors on request).

We have assumed lithium levels to remain relatively stable in drinking water over time based on the following. Firstly, that the element lithium is highly reactive and occurs in nature bound in minerals. It leaches slowly into groundwater from rocks and levels are known to vary geographically according to composition of rock with a low tendency to fluctuation over time.[24] Other authors have noted that groundwater lithium levels are unchanged following waterworks treatment to produce drinking water.[25] Secondly, previous authors have also assumed lithium to remain constant in the water supply over time.[17,26] Knudsen et al,[26] in their Danish study, based their assumption on lithium measurements from seven waterworks which demonstrated stability over a four year period, and from statistical analysis of existing measurements conducted on groundwater from 1947 to 2012. Thirdly, we obtained unpublished data held by the British Geological Society, which documents lithium samples from 14 sites in England collected at various timepoints between March 2007-March 2008 (further information available from authors on request). Repeated measurements did display a small variation in lithium level over time, but to a much lesser extent that the variation seen between sites. Furthermore, the theoretical timeframe for lithium to exert any protective effect against dementia in humans is unknown. It is usually assumed that long term exposure to environmental factors is important for dementia risk, however, it is possible that lithium exerts more acute effects. Our study was unable to take into account change of residential location, but again the timeframe of lithium ingestion for effect is unknown. Future work may benefit from establishing at least two time points at which cases resided in one geographical location.

Our large cohort sample was adjusted for IQ age 11 and stratified by gender. Control of other confounders was not possible due to the historical nature of the cohort and availability of data. Previous studies have been criticized for failing to take into account other dietary sources of lithium such as grains or green vegetables.[27] Lithium may enter foodstuffs through soil or via drinking water during cooking.[28] Local food sources are likely to reflect environmental lithium levels but additional sources can be gained from foods imported from areas with higher lithium levels. It is not possible to gain these data at a population level and as a result we were unable to consider these factors.

In common with other studies in this field it was not possible to take into account the potential effect of consumption of bottled water. In this cohort, born in 1921, it is assumed that consumption of

bottled water during their middle life would have been low. In 2006, a government survey revealed that two-thirds of individuals in Scotland drank mostly tap water rather than bottled water.[29] We postulate that the effect on our cohort would be negligible.

Access to healthcare in order to receive a diagnosis of dementia is a further potential confounder. In Scotland access to the National Health Service has been universal since 1948. As a result the authors have assumed that access to a dementia diagnosis is reasonably consistent across the country, although regional variations in practice cannot be accounted for. Dementia has been a priority for health improvement in Scotland since 2007 and in 2008 the Scottish Government launched a national target to improve the rate of diagnosis of dementia. By 2013 the rate of diagnosis had improved to 64% of the expected projected European estimated prevalence, and by 2016 had increased to 74% compared to 69% for the UK as a whole.[30] Our methodology for identifying cases using health records and diagnosis recorded at death could underestimate incidence though is similar to the method reported in the Danish study.[17] Our data does not include age of diagnosis and as a result is not designed to assess the potential of lithium to delay onset of dementia, though this remains an important question for future work. Statistical analysis by decile and quartile may have resulted in limited power to detect variation.

4.4 | Implications: Evidence for a threshold effect?

One explanation for our results is that the lithium level in drinking water in Scotland lies below a threshold for protective effect. Previous authors have suggested a minimum of 30 μg/L for reduced dementia risk. Compared with drinking water in Europe and other areas of the world the observed lithium mean level and range in Scottish water is much lower. As demonstrated in Table 2 which summarises all the existing studies regarding lithium in drinking water and dementia risk known to the authors at the time of writing.[17–19,31] One large study from the USA[31] (Table 2) found unadjusted rates of Dementia were significantly lower in areas of high drinking water lithium, but after adjustment for county level demographics and health care resources there was no benefit for Dementia or mental health outcomes.

The levels of lithium which can be present in drinking water are 100–1000 times lower than the doses with proven efficacy for mood disorders, which has posed controversy regarding whether any physiological effect can be expected at such low levels. Some biological action of lithium at low levels has been suggested by several papers investigating the relationship between lithium in drinking water and risk of suicide. Lithium levels in an east of England study[32] were similar to this present study, from 0.1 to 21 μg/L and described no association of suicide rates with lithium level. Kapusta et al,[28] in a cohort study of the Austrian population, failed to find a protective effect at lithium levels below 31 μg/L. Studies in this field have been criticized for failing to adequately address confounders[33] However Kapusta et al[28] did control for socioeconomic status, population density and access to health services and reported a reduced risk of suicide with higher lithium levels up to 1300 μg/L. A further study using data from the Texas public water supply also described a protective effect for lithium against suicide, while controlling for socioeconomic factors.[34]

It is suggested that multiple and diverse actions of lithium are critical for its therapeutic effects.[8] The Texas study by Fajardo et al[18] found that obesity and type 2 diabetes rates both correlated with the primary outcome of AD mortality and negatively correlated with low lithium level in drinking water. This is a particularly interesting finding in view of the known role of the GSK-3 enzyme in both obesity and Diabetes type 2 and the inhibitory effect of lithium on the enzyme which is postulated to underlie beneficial effects. The dose thresholds at which lithium exerts action on GSK-3 and other neuroprotective pathways, and influences tau and amyloid deposition in humans are not clear, but due to the complex actions of lithium, may differ to those responsible for therapeutic benefit at higher doses. Improved understanding of the clinical effect of low dose lithium and underlying mechanisms is potentially important for therapeutics in both functional and degenerative psychiatric disorder.

TABLE 2 Summarised key data of existing studies reporting lithium levels in drinking water and association with dementia.

Author (year), location	Outcome measure	Sample size	Li mean (μ/L)	Li range (μ/L)	Effect estimate (dementia risk)
Kessing et al. (2017) Denmark	Dementia diagnosis	73,731	-	0.6–30.7	Decreased risk above 10 μg/L, increased risk for intermediate levels 5.1–10 μg/L
Parker et al. (2018) USA	Bipolar disorder, dementia, or major depressive disorder diagnosis	4,227,556	27.4	0 to 40	No significant association after adjustment for demographics and health care resources
Fajardo et al. (2018) Texas	Dementia (AD) mortality rate	-(Population of 234 counties)	56	3–539	Decreased risk above 30 μg/L
Muronaga et al. (2022) Japan	Dementia	(Population of 808 regions)	2.39	-	No association on crude model. Adjusted model demonstrated decreased risk with higher lithium level for females but not males
Our study, Scotland	Dementia diagnosis	38,000	1.45	0.55–18.2	No association in males, increased risk in females at low-moderate levels

In conclusion, our study describes a very low level of lithium in drinking water in Scotland, at a level below that required for effect in previous research studies. Our study did not observe a reduced rate of all cause dementia with exposure to lithium levels up to 9.19 μg/L in drinking water in Scotland. However, we found a trend to increased risk for females at moderate concentrations oflithium compared to the lowest levels. A non-linear relationship with dementia risk has also been described previously by one Austrian study[17] and the reasons for this are currently not understood.

Confounder adjustment was limited to IQ age 11 due to the nature of our cohort sample. Future work investigating populations subject to a wide range of lithium levels would be valuable with careful consideration of confounders, though is extremely challenging in this research area. One major issue is that the contribution of drinking water to overall intake may be small compared to that obtained from foodstuffs. This factor may account for the variation which is seen between study outcomes. Consideration should also be made to meteorological factors which may be linked to lithium level which may account for the lower dementia rates seen in lithium rich areas, for example, sunshine hours Further work to investigate the longitudinal effects of low dose lithium is indicated to better understand the therapeutic mechanisms of lithium relevant to both functional and degenerative disease.

AUTHOR CONTRIBUTIONS

Ashleigh C. Duthie designed the study and wrote the manuscript. Jean Hannah, Ian J. Deary, and John M. Starr collated the original cohort data. Tom C. Russ undertook the statistical analysis. Daniel J. Smith initiated the data request from Scottish Water. All authors contributed to and have approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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