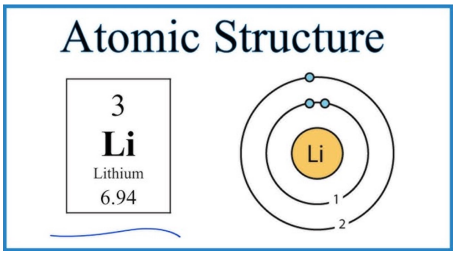
Lithium



Because it is highly reactive, lithium does not exist freely in its pure metallic form in nature. Instead, it occurs locked in salts and is commercially extracted from two primary sources:

•**Continental Brines:** Lithium-rich groundwater found in arid salt flats or "salars." The "Lithium Triangle"—spanning Bolivia, Chile, and Argentina—hosts nearly 50% of the world's resources.

•**Pegmatites (Hard Rock):** Igneous rocks containing valuable lithium-bearing minerals like spodumene. Australia is the leading global producer via this method.

Trace Sources in Nature

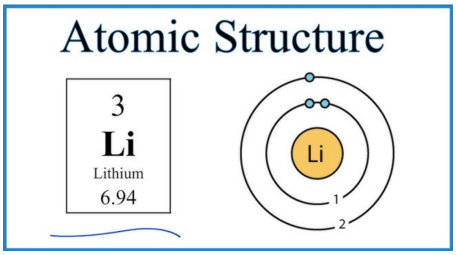
While brine and hard rock dominate commercial mining, lithium is widely distributed across the Earth's crust in low concentrations:

•**Water:** Present in seawater, underground geothermal wells, and even low concentrations in trace drinking water.

•**Food & Soil:** Trace amounts of lithium naturally occur in food sources such as cereal grains, nuts, and certain fruits and vegetables.

1

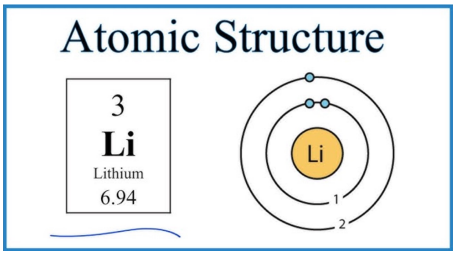
Lithium



- The average adult human body contains a very small amount of lithium—just **7 milligrams** in a 70 kg (154 lb) person
- It is not produced by the body and is instead a trace nutrient obtained directly from the environment through your daily diet and local drinking water.
- Most of this trace mineral naturally accumulates in your brain, kidneys, and bones. Dietary sources of lithium include:
- Lithium content in plants can vary, with grains and vegetables accumulating up to 4.6 µg/g of lithium, in addition to other lithium-rich sources like coriander leaves, tomatoes, garlic, nutmeg, and cumin seeds. Significantly lower levels of lithium can be found in onions, green chilies, cauliflower, rice, and mushrooms.
- The water source can also determine lithium levels.
- Nuts are particularly rich in lithium, with estimated concentrations of 1.09 and 3.12 µg/g in cashew nuts and walnuts, respectively[5]. Sunflower seeds, hazelnuts, and pine nuts are also notable sources of dietary lithium.

2

Lithium



- It plays a critical role in brain cell protection, mood stabilization, and the prevention of cognitive decline
- An electron donor with anti-oxidant properties
- At a microscopic level, it promotes neuron growth, balances neurotransmitters, and shields the brain from inflammation.
- Trace, dietary amounts of lithium (found naturally in drinking water and certain foods) are linked to neuroprotection. It stimulates the production of brain-derived neurotrophic factor (BDNF), a protein responsible for brain plasticity, learning, and memory.
- Ongoing research suggests that lithium supports long-term cognitive health. By inhibiting an overactive enzyme known as GSK-3, lithium can help shield the brain against the development of harmful protein plaques and neurofibrillary tangles associated with Alzheimer's disease.
- Beyond the brain, emerging studies indicate that low-dose lithium supplementation may support bone formation, fracture healing, and help mitigate diet-induced obesity.

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REVIEW

Lithium Therapeutic Functions: An Update on Pharmacokinetics, Pathophysiological Mechanisms of Action, Toxicity, and Side Effects

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Received: 8 November 2025 / Accepted: 3 January 2026

Abstract
Lithium is the most commonly used medicine to treat bipolar disorder (BD). It is considered a mood regulator, and the mechanisms underlying this effect still need to be elucidated. Some modulations are involved in neuroprotection, including neuronal communication, neuron differentiation and survival, synaptic modulation and plasticity, modulation of cognition, contribution to antioxidant defense, and reduction of inflammation, glial dysfunction, and apoptosis. In general, about 50% of the concentrations in serum are in the brain. However, it is essential to note that many gene expression differences influence the concentrations and actions of individuals. This review discusses the various mechanisms of lithium in BD I and II, its effects on neurotransmitters and receptors, the hypothalamic–pituitary–adrenal (HPA) axis, inflammation and neuroinflammation, immune functions, oxidative and nitrosative stress, mitochondrial respiratory chain function, intracellular signaling, and brain plasticity, as well as toxicity and side effects.

Keywords Lithium · Bipolar disorder · Mood regulator

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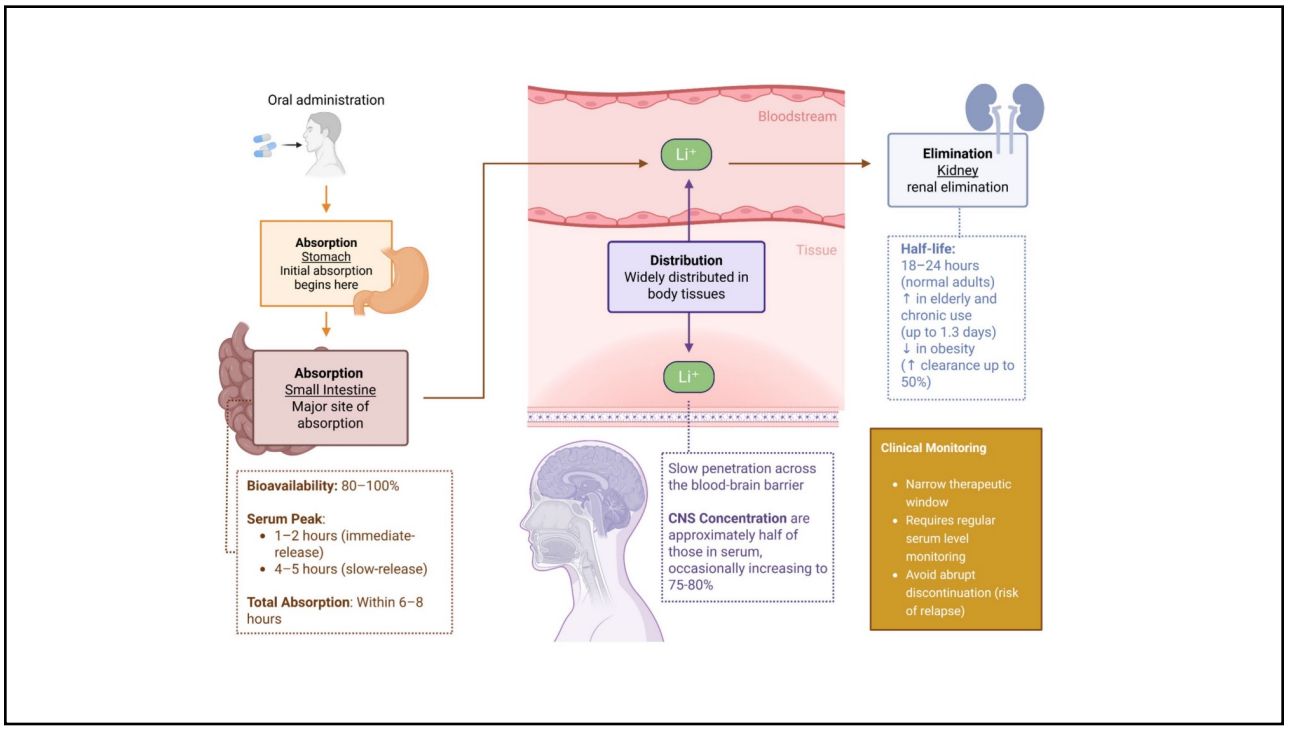
Oral administration
Absorption
Stomach
Initial absorption begins here
Absorption
Small Intestine
Major site of absorption
Bioavailability: 80–100%
Serum Peak:
1–2 hours (immediate-release)
4–5 hours (slow-release)
Total Absorption: Within 6–8 hours
Bloodstream
Li+
Tissue
Distribution
Widely distributed in body tissues
Li+
Slow penetration across the blood-brain barrier
CNS Concentration are approximately half of those in serum, occasionally increasing to 75-80%
Elimination
Kidney
renal elimination
Half-life:
18–24 hours (normal adults)
↑ in elderly and chronic use (up to 1.3 days)
↓ in obesity (↑ clearance up to 50%)
Clinical Monitoring
Narrow therapeutic window
Requires regular serum level monitoring
Avoid abrupt discontinuation (risk of relapse)

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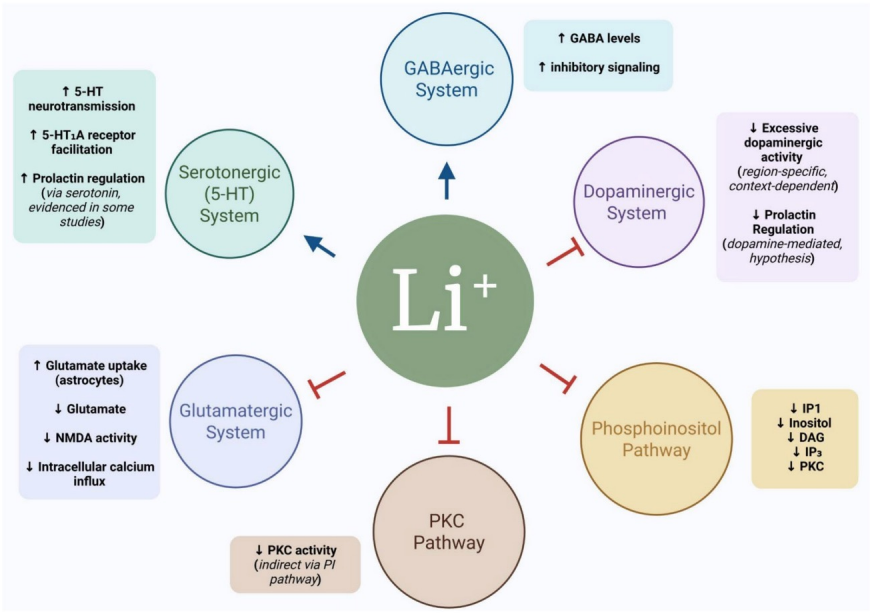
GABAergic System
↑ GABA levels
↑ inhibitory signaling
↑ 5-HT neurotransmission
↑ 5-HT1A receptor facilitation
↑ Prolactin regulation (via serotonin, evidenced in some studies)
Serotonergic (5-HT) System
Dopaminergic System
↓ Excessive dopaminergic activity (region-specific, context-dependent)
↓ Prolactin Regulation (dopamine-mediated, hypothesis)
Li+
↑ Glutamate uptake (astrocytes)
↓ Glutamate
↓ NMDA activity
↓ Intracellular calcium influx
Glutamatergic System
Phosphoinositol Pathway
↓ IP1
↓ Inositol
↓ DAG
↓ IP3
↓ PKC
PKC Pathway
↓ PKC activity (indirect via PI pathway)

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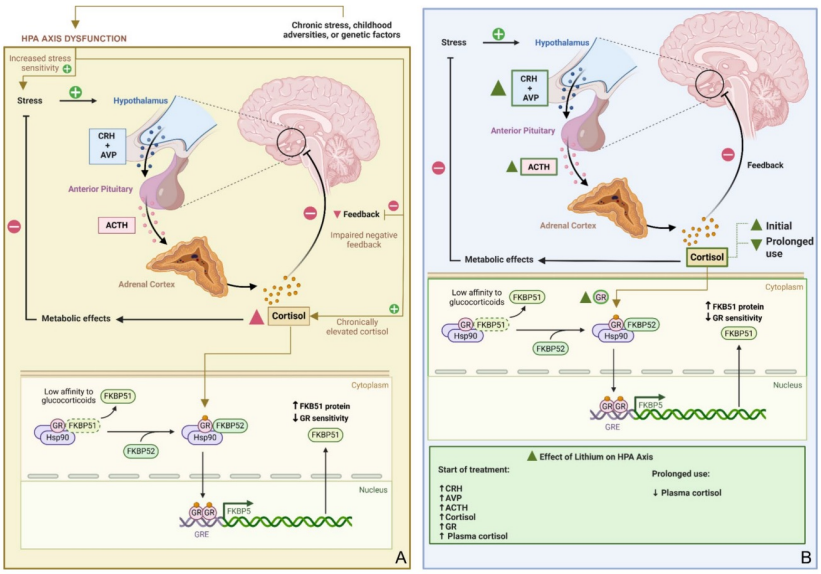

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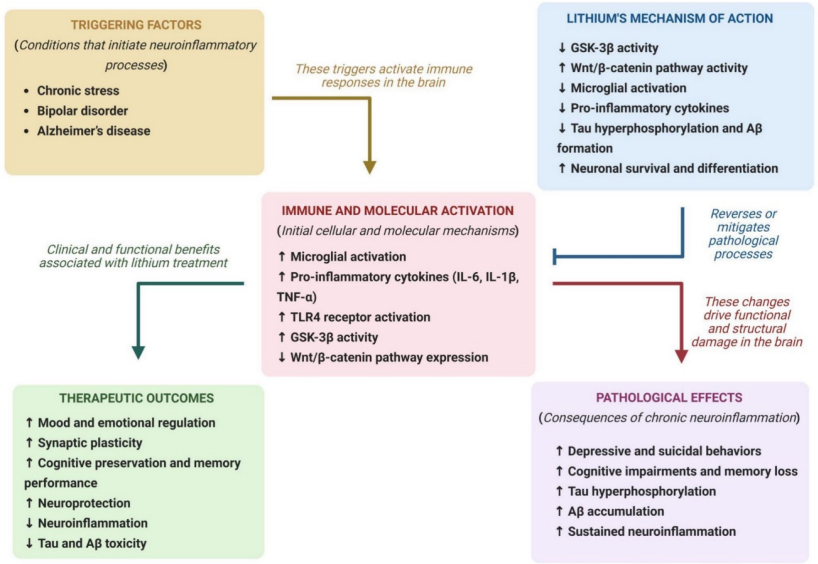

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PLOS MEDICINE

RESEARCH ARTICLE

Association between lithium use and the incidence of dementia and its subtypes: A retrospective cohort study

Shanqua Chen[1]*, Benjamin R. Underwood[1,2], Peter B. Jones[1,2,3], Jonathan R. Lewis[2], Rudolf N. Cardinal[1,2]

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OPEN ACCESS

Citation: Chen S, Underwood BR, Jones PB, Lewis JR, Cardinal RN (2022) Association between lithium use and the incidence of dementia and its subtypes: A retrospective cohort study. PLoS Med

Abstract

Background

Dementia is the leading cause of death in elderly Western populations. Preventative interventions that could delay dementia onset even modestly would provide a major public health impact. There are no disease-modifying treatments currently available. Lithium has been pro[Screenshot]otential treatment. We assessed the association between lithium use and

- We found that lithium was associated with a lower risk of receiving a diagnosis of dementia, including a lower risk of being diagnosed with either AD or VD.
- The extended analysis by the duration of lithium treatment indicated that both short- (≤1-year exposure) and long-term (>5-year exposure) lithium exposure (but not medium term, 1- to 5-year lithium exposure) was associated with decreased incidence of dementia and its subtypes. Power was less for the intermediate durations. There was some evidence for additional benefit with longer exposure durations.

What do these findings mean?

- Our findings support the possibility that lithium treatment could decrease the risk of developing dementia and supports the need for further randomised controlled trials (RCTs) to test the efficacy of lithium as a disease-modifying drug in dementia.
- The main limitation is that 73% of the patients in lithium-exposed group had mania/bipolar affective disorder (BPAD), which is a significant risk factor for dementia. Our results were in the opposite direction, however, and were supported by sensitivity analyses.

Author summary

Why was this study done?

- Dementia is the leading cause of death and disability in elderly Western populations.
- Preventative interventions that could delay dementia onset even modestly would provide a major public health impact.
- Lithium has been proposed as a potential treatment, but limited population-level research has been conducted to support the idea that lithium might delay the onset of dementia.

What did the researchers do and find?

- We identified 548 patients who were exposed to lithium and 29,070 patients who were not exposed to lithium between January 1, 2005 and December 31, 2019, using data from electronic clinical records of secondary care mental health (MH) services in Cambridgeshire and Peterborough NHS Foundation Trust (CPFT), UK.
- We assessed the association between lithium use and the incidence of dementia and its subtypes, including Alzheimer disease (AD) and vascular dementia (VD).

PLOS Medicine | https://doi.org/10.1371/journal.pmed.1003941 March 17, 2022

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Clinical and biological effects of long-term lithium treatment in older adults with amnestic mild cognitive impairment: randomised clinical trial

Orestes V. Forlenza, Márcia Radanovic, Leda L. Talib and Wagner F. Gattaz

Background

Experimental studies indicate that lithium may facilitate neurotrophic/protective responses in the brain. Epidemiological and imaging studies in bipolar disorder, in addition to a few trials in Alzheimer's disease support the clinical translation of these findings. Nonetheless, there is limited controlled data about potential use of lithium to treat or prevent dementia.

Aims

To determine the benefits of lithium treatment in patients with amnestic mild cognitive impairment (MCI), a clinical condition associated with high risk for Alzheimer's disease.

Method

A total of 61 community-dwelling, physically healthy, older adults with MCI were randomised to receive lithium or placebo (1:1) for 2 years (double-blind phase), and followed-up for an additional 24 months (single-blinded phase) (trial registration at clinicaltrials.gov: NCT01055392). Lithium carbonate was prescribed to yield subtherapeutic concentrations (0.25–0.5 mEq/L). Primary outcome variables were the cognitive (Alzheimer's Disease Assessment Scale – cognitive subscale) and functional (Clinical Dementia Rating – Sum of Boxes) parameters obtained at baseline and after 12 and 24 months. Secondary outcomes were neuropsychological test scores; cerebrospinal fluid (CSF) concentrations of Alzheimer's disease-related biomarkers determined at 0, 12 and 36 months; conversion rate from MCI to dementia (0–48 months).

Results

Participants in the placebo group displayed cognitive and functional decline, whereas lithium-treated patients remained stable over 2 years. Lithium treatment was associated with better performance on memory and attention tests after 24 months, and with a significant increase in CSF amyloid-beta peptide ($A\beta_{1-42}$) after 36 months.

Conclusions

Long-term lithium attenuates cognitive and functional decline in amnestic MCI, and modifies Alzheimer's disease-related CSF biomarkers. The present data reinforces the disease-modifying properties of lithium in the MCI–Alzheimer's disease continuum.

Declaration of interest

None.

Key words

Alzheimer's disease; mild cognitive impairment; treatment; clinical trial; lithium.

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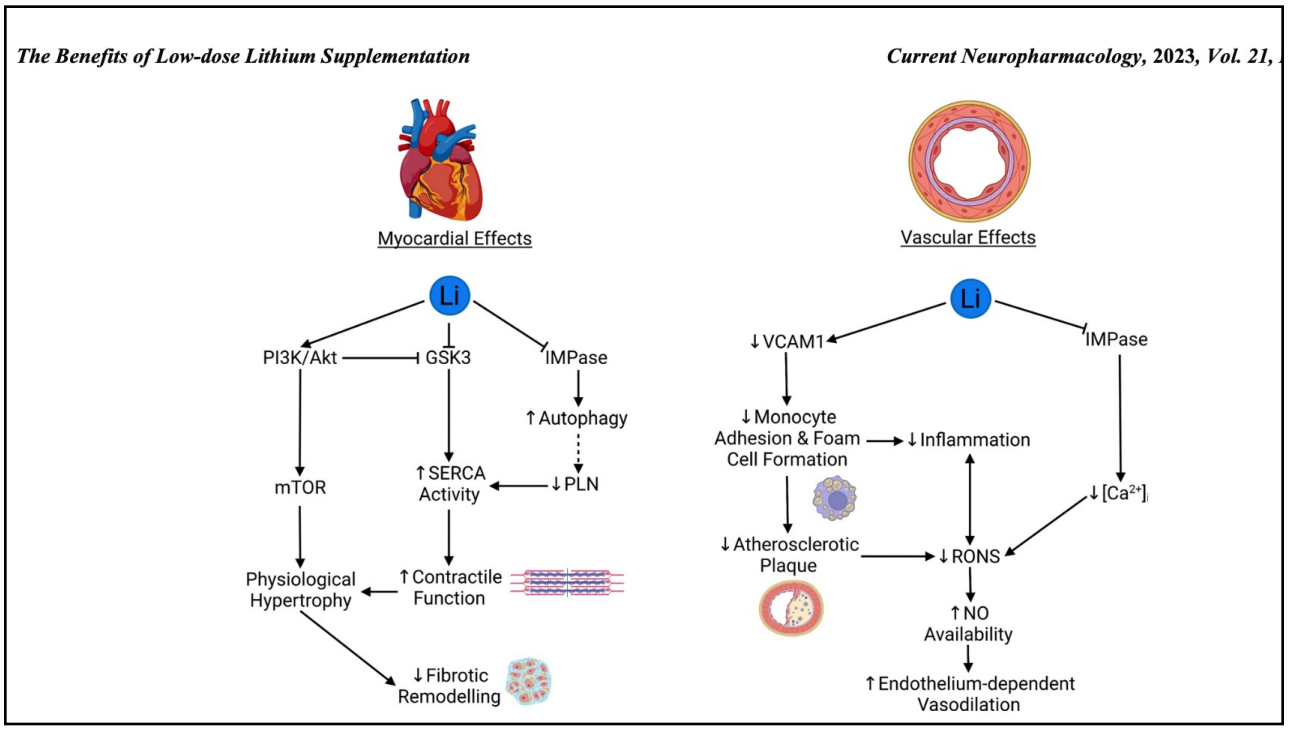

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JAMA Neurology | Original Investigation

Low-Dose Lithium for Mild Cognitive Impairment
A Pilot Randomized Clinical Trial

Ariel G. Gildengers, MD; Tamer S. Ibrahim, PhD; Stewart J. Anderson, PhD; James E. Emanuel, BS; Tales Santini, PhD; Jihui L. Diaz, PhD; Brian J. Lopresti, MS; Sarah K. Royse, PhD; Oscar L. Lopez, MD; Xuemei Zeng, PhD; Bruno de Almeida, MSc; Salem K. Alkhateeb, BS; Cong Chu, BS; Thomas K. Karikari, PhD; Laisze Lee, MA; Andrea M. Weinstein, PhD; Meryl A. Butters, PhD

Supplemental content

IMPORTANCE Lithium deficiency may contribute to Alzheimer disease pathogenesis. No randomized clinical trial has examined lithium's effects on cognition, neuroimaging, and plasma biomarkers in mild cognitive impairment (MCI).

OBJECTIVE To examine the feasibility, safety, and preliminary efficacy of lithium carbonate for delaying cognitive decline in older adults with MCI.

DESIGN, SETTING, AND PARTICIPANTS This single-site, randomized, double-blind, placebo-controlled pilot feasibility clinical trial was conducted at the University of Pittsburgh School of Medicine from February 2018 to August 2024, with 2-year follow-up. Analyses used linear mixed-effects models in the intention-to-treat population. Adults aged 60 years or older with MCI who were free of major psychiatric or neurologic illness and contraindications to lithium were included. Of 170 individuals assessed, 83 were randomized (41 lithium vs 42 placebo), with 80 starting treatment (41 lithium vs 39 placebo). Data were analyzed from August 2024 to December 2025.

INTERVENTION Daily low-dose lithium carbonate or placebo for 2 years.

MAIN OUTCOMES AND MEASURES Six prespecified coprimary outcomes included cognitive performance (California Verbal Learning Test-II [CVLT-II] delayed recall, Brief Visuospatial Memory Test-Revised, preclinical Alzheimer cognitive composite), hippocampal volume,

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Examining the Relationship between Trace Lithium in Drinking Water and the Rising Rates of Age-Adjusted Alzheimer's Disease Mortality in Texas

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[b]*Department of Actuarial Sciences, University of Waterloo, Waterloo, ON, Canada*
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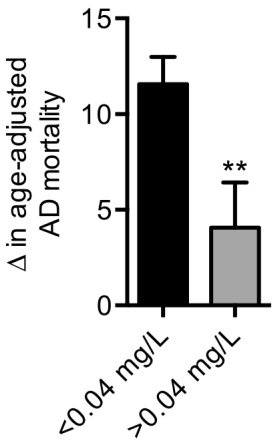
[d]*Centre for Neuroscience, Brock University, St. Catharines, ON, Canada*

Handling Associate Editor: William Grant

Accepted 11 September 2017

Abstract.
Background: Alzheimer's disease (AD) mortality rates have steadily increased over time. Lithium, the current gold standard treatment for bipolar disorder, can exert neuroprotective effects against AD.
Objective: We examined the relationship between trace levels of lithium in drinking water and changes in AD mortality across several Texas counties.
Methods: 6,180 water samples from public wells since 2007 were obtained and averaged for 234 of 254 Texas counties.



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