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Lithium, Mortality, and Longevity: From Conventional Psychiatric Treatment to Environmental Exposure and Microdose Supplementation — A Critical Review

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Abstract

Background: Lithium is an established treatment for bipolar disorder and has been associated with favorable mortality outcomes in psychiatric populations. Environmental epidemiological studies and experimental investigations have also raised interest in its possible effects on neurodegeneration, biological aging, and longevity. These observations have stimulated research into low-dose and microdose lithium exposure, although their clinical significance remains uncertain.

Objective: To critically evaluate the evidence linking lithium exposure to mortality, cognitive aging, and longevity, with particular emphasis on the biological rationale, clinical evidence, and safety of microdose supplementation.

Methods: A critical narrative review was conducted using targeted searches of peer-reviewed biomedical literature, trial registries, and selected grey literature. Randomized trials, observational studies, ecological investigations, systematic reviews, and experimental reports were examined. Evidence was interpreted according to study design, exposure category, clinical outcomes, and methodological limitations.

Results: Conventional lithium treatment has been associated with lower all-cause mortality in patients with mood disorders, although these findings cannot establish a direct anti-aging effect. Environmental studies have reported inverse associations between trace lithium exposure and mortality or dementia-related outcomes, but results are inconsistent. Small clinical studies of low-dose lithium have suggested possible cognitive benefits, whereas more recent trials and meta-analyses have yielded inconclusive or negative findings. Experimental investigations implicate glycogen synthase kinase-3, autophagy, oxidative stress responses, and endogenous brain lithium homeostasis. A 2025 study identified reduced lithium availability in human brain tissue affected by cognitive impairment and demonstrated favorable effects of lithium replacement in mouse models. However, no randomized clinical trial has demonstrated that microdose lithium supplementation reduces all-cause mortality or extends human lifespan.

Conclusions: Lithium represents a biologically plausible candidate for further investigation in geroscience. Nevertheless, therapeutic mortality benefits, environmental associations, and experimental findings cannot be directly extrapolated to preventive microdose supplementation. Clinical efficacy, optimal exposure, and long-term safety remain unresolved.

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1. Introduction

Lithium has occupied a distinctive position in medicine since its introduction as a treatment for mood disorders. Its established role in bipolar disorder is supported by decades of clinical research, yet its biological actions extend beyond mood stabilization. Lithium influences intracellular signaling, neuronal survival, inflammatory pathways, and cellular homeostasis, providing a rationale for investigating its potential relevance to neurodegeneration and aging. The presence of naturally occurring lithium in drinking water and food has further stimulated interest in whether exposures substantially below conventional therapeutic levels

might influence human health ^[1, 2].

The relationship between lithium and mortality constitutes an important starting point for this discussion. Patients with bipolar disorder experience increased mortality compared with the general population, reflecting psychiatric and physical health burdens. In a systematic review and meta-analysis of randomized trials, Cipriani *et al.* reported lower all-cause mortality among lithium-treated participants than among those receiving placebo ^[3]. Subsequent population-based investigations have also identified associations between sustained lithium treatment and improved survival ^[4, 5]. These findings are clinically important but do not establish that lithium directly slows biological aging.

The possibility of an anti-aging effect has been examined more directly in observational research. Mutz *et al.* investigated lithium treatment duration, telomere length, frailty, metabolomic age, and mortality using UK Biobank data. Their findings did not support a consistent association between treatment duration and the evaluated biological aging markers or all-cause mortality ^[6]. This negative investigation is particularly relevant because it challenges the assumption that long-term exposure necessarily produces measurable anti-aging effects.

Environmental epidemiology has generated a separate body of evidence. Zarse *et al.* reported an inverse association between naturally occurring lithium concentrations in drinking water and all-cause mortality across Japanese municipalities ^[7]. Fajardo *et al.* subsequently identified a similar association in Texas counties ^[8]. These findings raised the possibility that trace lithium exposure might influence survival at concentrations far below those associated with conventional psychiatric treatment. However, ecological investigations cannot establish individual-level causality and remain vulnerable to geographic, socioeconomic, dietary, and environmental confounding.

Interest in lithium and cognitive aging has developed in parallel. A nationwide Danish investigation identified a nonlinear association between drinking-water lithium concentrations and dementia incidence ^[9]. Conversely, a Scottish cohort study did not demonstrate a protective association at the very low concentrations measured ^[10]. A subsequent systematic review of environmental lithium and dementia highlighted potentially favorable findings in some populations while acknowledging the limitations of the observational evidence ^[11].

Clinical research has also explored whether lower lithium exposures might modify cognitive decline. Nunes *et al.* reported stabilization of cognitive performance in patients with Alzheimer disease receiving a microdose intervention ^[12]. Other randomized studies involving higher but subtherapeutic lithium exposures have reported potentially favorable cognitive or biomarker outcomes ^[13, 14]. Nevertheless, systematic reviews and more recent trials have demonstrated substantial heterogeneity and inconsistent results ^[15–19].

A particularly important development occurred in 2025, when Aron *et al.* reported reduced endogenous lithium availability in human brain tissue affected by mild cognitive impairment and Alzheimer disease. Experimental lithium depletion accelerated neuropathological changes in mice, whereas lithium replacement using an orotate formulation produced favorable effects on brain pathology and memory ^[21]. These findings introduced a new hypothesis: disturbances in endogenous lithium homeostasis might contribute to

neurodegenerative processes.

However, this hypothesis must be distinguished from the claim that oral supplementation with approximately 1 mg of elemental lithium daily improves longevity. Experimental restoration of lithium homeostasis, treatment of established psychiatric disease, and supplementation of healthy individuals represent fundamentally different interventions. Moreover, lithium has recognized renal, thyroid, and other adverse effects at conventional therapeutic exposures, and the long-term safety of deliberate microdose supplementation remains insufficiently characterized ^[25, 26].

The present review critically integrates these different bodies of evidence, beginning with conventional lithium treatment and mortality, examining environmental epidemiology and neurodegeneration, and concluding with a focused assessment of microdose lithium and longevity. Particular attention is given to conflicting findings, exposure standardization, biological plausibility, safety, and the distinction between established clinical benefits and hypotheses requiring further investigation.

2. Methods

2.1. Review Design

This study was designed as a critical narrative review integrating clinical, epidemiological, experimental, and translational evidence concerning lithium exposure, mortality, neurodegeneration, and biological aging. The review was organized around four principal questions: whether conventional lithium treatment is associated with reduced mortality; whether environmental lithium exposure correlates with mortality or age-related outcomes; whether lower lithium exposures have demonstrated clinically meaningful neuroprotective effects; and whether available evidence supports microdose lithium as a potential longevity intervention.

The review was not designed as a systematic review or meta-analysis. Consequently, no pooled effect estimates were calculated, and no claims of exhaustive study identification, formal PRISMA compliance, or comprehensive risk-of-bias assessment were made.

2.2. Literature Identification

Targeted searches were conducted using biomedical literature sources, including PubMed-indexed publications, journal websites, reference lists of relevant reviews, and publicly accessible trial registries. Search concepts included lithium, mortality, longevity, lifespan, biological aging, bipolar disorder, drinking water, environmental exposure, dementia, Alzheimer disease, mild cognitive impairment, microdose lithium, low-dose lithium, lithium orotate, glycogen synthase kinase-3, and autophagy.

Randomized controlled trials, observational cohorts, ecological investigations, systematic reviews, and experimental studies were considered when they addressed one or more of the review questions. Selected grey literature included clinical trial registrations, published study protocols, institutional research communications, and commercial educational material. Grey-literature findings were distinguished from peer-reviewed clinical results.

Because the searches were targeted rather than conducted through a fully documented systematic protocol, database-specific record counts, screening totals, and exclusion frequencies are not reported.

2.3. Evidence Appraisal

Evidence was interpreted according to study design, population, exposure definition, comparator, follow-up duration, outcome measurement, and potential sources of bias. Randomized clinical trials were prioritized when evaluating efficacy, whereas observational and ecological investigations were considered primarily for hypothesis generation.

Particular attention was given to distinguishing elemental lithium content from lithium salt mass, administered dose from serum concentration, and environmental concentration from individual intake. Findings from experimental organisms were interpreted as mechanistic evidence rather than direct proof of human clinical benefit.

2.4. Evidence Synthesis

The findings were synthesized narratively according to clinical and biological context. Mortality outcomes were distinguished from cognitive outcomes and surrogate markers of biological aging. Positive, negative, and inconclusive studies were considered together, and the implications of publication bias, residual confounding, and incomplete reporting were addressed.

3. Results

3.1. Conventional Lithium Treatment and All-Cause Mortality

The most substantial clinical evidence linking lithium to mortality originates from patients with mood disorders. Cipriani *et al.* evaluated 48 randomized controlled trials involving 6,674 participants and reported lower all-cause mortality among lithium-treated individuals compared with placebo (OR 0.38; 95% CI 0.15–0.95) [3]. Although this result supports a potential survival advantage, the relatively small number of mortality events limits precision.

A nationwide Taiwanese cohort study involving 25,787 patients with bipolar disorder also identified favorable mortality associations among patients receiving mood stabilizers. Lithium was associated with the lowest adjusted risks of all-cause and natural mortality among the evaluated treatments [4]. More recently, Oliva *et al.* analyzed 15,384 patients with bipolar disorder in Catalonia and reported that sustained lithium exposure was associated with lower all-cause mortality compared with no exposure (HR 0.69; 95% CI 0.51–0.93) [5].

These findings support the clinical importance of sustained lithium treatment in appropriately selected psychiatric populations. Nevertheless, observational treatment continuity may also reflect adherence, healthcare engagement, disease severity, and other factors associated with survival. Consequently, the available evidence does not establish that lithium independently modifies biological aging.

3.2. Lithium Exposure and Biological Aging Markers

Mutz *et al.* investigated whether the duration of lithium treatment was associated with markers of biological aging and mortality in UK Biobank participants. Among 591 individuals who had received lithium prescriptions, treatment duration was not significantly associated with telomere length, frailty, or metabolomic age. Lithium treatment duration also did not predict all-cause mortality [6].

This study provides an important counterpoint to the broader longevity hypothesis. Although observational limitations remain, its findings indicate that favorable mortality

associations in psychiatric populations should not automatically be interpreted as evidence of slower biological aging.

3.3. Environmental Lithium Exposure and Population Mortality

Zarse *et al.* examined drinking-water lithium concentrations across 18 Japanese municipalities encompassing approximately 1.2 million residents. Higher lithium concentrations were inversely associated with age- and sex-adjusted mortality. The investigators also reported increased lifespan in *Caenorhabditis elegans* exposed experimentally to lithium [7].

Fajardo *et al.* subsequently evaluated environmental lithium concentrations across Texas counties. Lithium concentrations were inversely correlated with all-cause mortality ($r = -0.18$; $p = 0.006$) and years of potential life lost ($r = -0.22$; $p = 0.001$) [8].

Although statistically significant, these correlations were modest. Geographic differences in lithium exposure may coexist with differences in socioeconomic conditions, environmental exposures, healthcare access, and population characteristics. Furthermore, environmental concentration does not directly establish individual lithium intake. These investigations therefore provide hypothesis-generating evidence rather than proof that supplementation extends human lifespan.

3.4. Environmental Lithium and Dementia-Related Outcomes

Kessing *et al.* examined long-term drinking-water lithium exposure and dementia incidence in Denmark. The study included 73,731 dementia cases and 733,653 controls and identified a nonlinear association between lithium exposure and dementia incidence [9]. Higher exposure categories were associated with lower dementia incidence in some comparisons, whereas intermediate exposure categories showed less favorable results.

In contrast, Duthie *et al.* investigated 37,597 participants from the Scottish Mental Survey 1932 cohort. The study did not identify a protective association between the very low lithium concentrations measured in drinking water and subsequent dementia risk. In women, some exposure categories were associated with increased rather than decreased dementia risk [10].

A systematic review by Fraiha-Pegado *et al.* synthesized five observational investigations of environmental lithium and dementia. Although several studies suggested potentially favorable associations, the evidence remained limited by heterogeneous exposure measurements, ecological or observational designs, and uncertain causal interpretation [11]. The conflicting findings indicate that the relationship between environmental lithium and dementia cannot be adequately described by a simple linear protective model.

3.5. Microdose Lithium in Alzheimer Disease

Nunes *et al.* conducted a randomized clinical investigation involving patients with Alzheimer disease who received a microdose lithium intervention or control treatment. The study evaluated cognitive performance over 15 months and reported relative stabilization of Mini-Mental State Examination scores in the lithium group, whereas scores declined in controls [12].

This investigation is particularly relevant because it directly

examined microgram-level lithium exposure rather than conventional psychiatric treatment. Nevertheless, the evidence remains preliminary. The trial was relatively small, the principal reported outcome was cognitive performance, and the findings have not established an effect on mortality, dementia prevention in healthy individuals, or lifespan extension.

A further limitation concerns formulation and dose reporting. The distinction between lithium salt mass and elemental lithium content is essential when interpreting very small exposures. Without standardized reporting and pharmacokinetic confirmation, direct comparisons between microdose studies remain difficult.

3.6. Low-Dose Lithium in Mild Cognitive Impairment

Forlenza *et al.* conducted a randomized controlled trial involving 45 patients with amnesic mild cognitive impairment. Lithium treatment was associated with favorable findings in selected cognitive measures and cerebrospinal fluid biomarkers, including phosphorylated tau ^[13]. A subsequent investigation by the same research group provided additional evidence suggesting possible benefits during longer-term treatment ^[14].

A 2015 meta-analysis by Matsunaga *et al.*, involving three randomized trials and 232 participants, reported a modest favorable effect of lithium on cognitive performance compared with placebo (standardized mean difference -0.41 ; 95% CI -0.81 to -0.02) ^[15].

However, more recent evidence has been less conclusive. In 2026, Gildengers *et al.* published a two-year randomized pilot trial involving 80 treated participants with mild cognitive impairment. None of the six prespecified coprimary outcomes reached the required statistical significance threshold. Although exploratory findings suggested possible differences in verbal memory decline, these results were insufficient to establish clinical efficacy ^[16].

A more recent systematic review and meta-analysis of lithium in Alzheimer dementia included six randomized trials involving 394 participants and did not identify consistent cognitive or functional benefits ^[17]. The differences between earlier favorable findings and more recent inconclusive results highlight the need for larger, methodologically rigorous investigations. Sage Journals

3.7. Broader Clinical Evidence Concerning Lower Lithium Exposures

Strawbridge *et al.* systematically reviewed lower-dose lithium interventions across neuropsychiatric conditions and identified preliminary signals of benefit in selected outcomes, particularly cognition. However, the included investigations were heterogeneous, and the evidence did not establish a role for lithium in longevity prevention ^[18].

A subsequent systematic review by Sabtiari *et al.* examined lithium-associated cognitive outcomes in adults and identified inconsistent effects across cognitive domains and clinical populations ^[19]. These findings reinforce the importance of distinguishing disease-specific effects from generalized cognitive enhancement.

Neal *et al.* investigated lithium detection in the human brain using lithium magnetic resonance imaging following lower-dose exposure in healthy participants.

The study demonstrated the feasibility of detecting brain lithium under the experimental conditions employed, providing a methodological contribution to future pharmacokinetic investigations ^[20]. However, it did not establish a clinical benefit.

3.8. Endogenous Brain Lithium and Alzheimer Disease

A major development in this field occurred in 2025 with the publication of the study by Aron *et al.* in *Nature*. The investigators reported reduced lithium availability in brain tissue from individuals with mild cognitive impairment and Alzheimer disease. In experimental mouse models, lithium depletion accelerated amyloid accumulation, tau-related abnormalities, neuroinflammation, and cognitive deterioration. Lithium replacement using an orotate formulation produced favorable effects on neuropathological and cognitive outcomes ^[21].

These findings suggest that endogenous lithium homeostasis may be biologically relevant to brain aging. However, the human component was observational, and the intervention experiments were conducted in mice. The results therefore cannot establish that lithium supplementation prevents Alzheimer disease in humans or that lithium orotate is clinically superior to other formulations.

Importantly, the study did not demonstrate that a particular daily oral microdose prolongs human life. Its principal contribution is the identification of a potentially important biological mechanism that requires clinical validation. Nature

3.9. Biological Mechanisms Potentially Relevant to Longevity

Lithium influences several intracellular pathways implicated in cellular homeostasis and neurodegeneration. Klein and Melton demonstrated that lithium inhibits glycogen synthase kinase-3, providing a molecular explanation for some of its diverse biological effects ^[22].

Autophagy represents another important pathway. Sarkar *et al.* demonstrated that lithium can induce autophagy through inhibition of inositol monophosphatase, independently of mammalian target of rapamycin signaling ^[23]. This mechanism is relevant to protein homeostasis and the cellular handling of aggregation-prone proteins.

Experimental lifespan investigations provide additional support for the biological plausibility of lithium-related effects on aging. Castillo-Quan *et al.* reported increased lifespan and improved health-related outcomes in *Drosophila*, involving GSK-3 and NRF2-dependent signaling ^[24]. However, the magnitude and direction of lithium effects may depend on experimental exposure, species, and biological context.

These findings demonstrate that lithium can influence mechanisms relevant to aging, but they do not establish that comparable effects occur in humans receiving microgram-level supplementation.

3.10. Lithium Orotate and Safety Considerations

Lithium orotate has received increasing attention because of its use in supplemental formulations and recent experimental findings. Murbach *et al.* conducted a toxicological evaluation involving genotoxicity testing and repeated-dose exposure in animals. The study did not identify major toxicity signals

under the investigated conditions ^[25].

Nevertheless, short-term animal toxicology cannot establish long-term safety in humans. Moreover, findings obtained with one lithium formulation cannot be generalized to all formulations or exposure levels.

The established safety literature concerning conventional lithium treatment includes renal, thyroid, and calcium-related adverse effects. McKnight *et al.* systematically reviewed the toxicity profile of lithium and emphasized the importance of considering these effects during long-term treatment ^[26].

For preventive supplementation, the relevant safety question is different: whether sustained exposure in individuals without psychiatric indications produces a favorable balance between potential benefits and risks. This question remains insufficiently answered.

3.11. Lithium and Substance Use Disorders

Lithium has also been investigated in substance use disorders, particularly alcohol dependence. Earlier studies produced inconsistent findings. A large randomized trial by Dorus *et al.* involving 457 participants did not demonstrate meaningful improvement in alcohol-related outcomes with lithium treatment ^[27]. Similarly, de la Fuente *et al.* reported no significant advantage over placebo in a controlled investigation of alcoholism ^[28].

These results do not support lithium as an established treatment for primary alcohol dependence. Moreover, evidence concerning conventional lithium treatment in substance use disorders cannot be extrapolated to microdose supplementation.

3.12. Negative Clinical Findings in Other Conditions

The importance of evaluating negative evidence is illustrated by a randomized trial of lithium aspartate in patients with neurological symptoms associated with long COVID. Guttuso *et al.* did not identify significant improvements in fatigue or cognitive dysfunction with the investigated intervention ^[29].

Although this study addressed a different clinical condition, it reinforces a broader principle: mechanistic plausibility does not guarantee clinical efficacy.

3.13. Environmental Lithium and Population Mental Health Outcomes

Ecological investigations have also examined lithium concentrations in drinking water in relation to population mental health outcomes. A systematic review and meta-analysis by Memon *et al.* reported an inverse association between environmental lithium concentrations and suicide mortality rates, although heterogeneity and ecological bias were substantial ^[30].

Eyre-Watt *et al.* similarly synthesized studies across numerous geographic regions and identified associations between higher environmental lithium concentrations and selected neuropsychiatric outcomes ^[31]. These observations remain relevant to population epidemiology but do not demonstrate the efficacy of individual supplementation.

3.14. Environmental Lithium and Alzheimer Mortality

Fajardo *et al.* examined trace lithium concentrations in drinking water and changes in age-adjusted Alzheimer disease mortality in Texas ^[32]. The findings suggested an

inverse association, although the ecological design prevented causal interpretation.

This study should be distinguished from investigations of all-cause mortality. Disease-specific mortality, dementia incidence, cognitive performance, and biological aging markers represent different endpoints and cannot be considered interchangeable measures of longevity.

3.15. Grey Literature and Registered Investigations

The grey-literature search identified several relevant research records. A Brazilian clinical trial registry entry describes a randomized investigation of lithium microdoses in Alzheimer disease, with planned longitudinal follow-up ^[33]. However, a registered protocol does not constitute evidence of efficacy, and the registry record alone does not establish that the planned outcomes were achieved.

A published Chilean study protocol describes a randomized investigation of lower-dose lithium for prevention of cognitive decline in patients with mood disorders ^[34]. Another registered study concerns an accessible lithium supplement in a psychiatric population ^[35]. These investigations demonstrate continued research interest but cannot be interpreted as positive clinical results in the absence of published outcome data.

Commercial educational literature, including the January 2026 article *Microdosing Lithium: Potential Benefits for Brain Health and Aging* in *Life Extension Magazine*, has also emphasized experimental neuroprotection and environmental epidemiology ^[36]. Such material is useful for identifying emerging claims and tracing cited studies, but it is not equivalent to independent clinical evidence. In particular, the recommendation of approximately 1 mg of elemental lithium daily is not supported by randomized evidence demonstrating reduced mortality or increased lifespan.

3.16. Overall Interpretation of The Microdose Longevity Hypothesis

The evidence supporting microdose lithium as a potential longevity intervention remains indirect. Favorable mortality findings originate primarily from psychiatric treatment populations, environmental epidemiology, and experimental organisms. Clinical investigations involving very small administered quantities have focused predominantly on cognitive or neuropsychiatric outcomes rather than mortality. The 2025 experimental findings concerning endogenous brain lithium provide a new mechanistic rationale for further investigation. However, no adequately powered randomized trial has established that microdose supplementation reduces all-cause mortality, prevents major age-related diseases, or extends human lifespan.

4. Discussion

The present review identifies a substantial difference between the established clinical role of lithium and its emerging application as a potential longevity-related intervention. Conventional lithium treatment has a well-developed evidence base in mood disorders, including favorable mortality findings from randomized and observational investigations. In contrast, the evidence supporting microdose supplementation in individuals without psychiatric indications remains preliminary.

The first important distinction concerns the interpretation of

mortality. Reduced mortality among patients receiving lithium for bipolar disorder may reflect improved management of a serious chronic disease rather than direct modification of aging. The favorable findings reported by Cipriani *et al.*, Chen *et al.*, and Oliva *et al.* should therefore be interpreted within their clinical contexts^[3–5]. The absence of significant associations between lithium treatment duration and several biological aging markers in the investigation by Mutz *et al.* further emphasizes that improved survival and slower biological aging are not synonymous^[6]. The second distinction concerns environmental exposure. Studies from Japan and Texas have reported inverse associations between trace lithium concentrations and mortality^[7,8]. These findings are intriguing because they suggest that lithium exposure may have biological relevance at concentrations substantially below conventional psychiatric treatment. However, ecological associations cannot establish individual-level causal effects. Geographic variation in lithium concentrations may coincide with differences in other environmental and population characteristics, and the available studies cannot determine whether deliberate supplementation would reproduce the observed associations.

The dementia literature demonstrates similar uncertainty. The Danish investigation identified a nonlinear association between environmental lithium and dementia incidence, whereas the Scottish cohort did not support a protective effect at the concentrations studied^[9,10]. These conflicting findings challenge the assumption of a simple dose–response relationship. They also suggest that environmental lithium research requires more precise exposure assessment and better control of individual-level confounding.

Clinical investigations of lower-dose lithium provide a more direct approach to evaluating potential neuroprotective effects. The findings reported by Nunes *et al.* are particularly relevant because the intervention involved a microgram-level exposure^[12]. However, the study was small, and its findings have not been established through large independent confirmatory trials. Earlier investigations by Forlenza *et al.* and the meta-analysis by Matsunaga *et al.* suggested possible cognitive benefits^[13–15], whereas more recent evidence has been less convincing^[16,17]. The absence of significant coprimary outcomes in the 2026 randomized pilot trial is especially important because it demonstrates the difference between exploratory signals and confirmed clinical efficacy. The 2025 study by Aron *et al.* introduces a potentially important conceptual shift^[21]. Rather than considering lithium exclusively as a pharmacological agent, the investigators explored the physiological relevance of endogenous lithium homeostasis in the brain. Their findings suggest that disturbances in lithium availability may contribute to neurodegenerative processes and that restoration of lithium homeostasis can influence pathology in experimental models. Nevertheless, this does not establish a clinically recognized lithium deficiency syndrome in humans, nor does it demonstrate that supplementation in individuals with normal lithium homeostasis provides benefit.

The mechanistic literature offers several plausible pathways through which lithium could influence age-associated biological processes. GSK-3 signaling, autophagy, protein homeostasis, and cellular stress responses are all relevant to

aging research^[22–24]. However, the concentrations required to modify these pathways in experimental systems may differ substantially from those achieved through trace environmental exposure or microdose supplementation. Establishing biological plausibility therefore represents only an early stage in evaluating a preventive intervention.

Another major challenge concerns exposure classification. The terms *low-dose*, *microdose*, and *trace lithium* have been applied inconsistently across publications. Studies may report elemental lithium, lithium salt mass, serum concentration, or environmental concentration without sufficient standardization. This heterogeneity limits comparisons and may contribute to inappropriate extrapolation of findings. Future investigations should use clearly defined exposure metrics and validated pharmacokinetic measurements.

Safety must also be considered within the appropriate clinical context. Conventional lithium treatment has recognized adverse effects, particularly involving renal and endocrine function^[26]. Although lower exposures may have different safety profiles, the available evidence does not establish the consequences of decades-long supplementation in otherwise healthy individuals. Short-term animal toxicology and the absence of a prominent reported safety signal are insufficient to demonstrate long-term safety.

The commercial promotion of microdose lithium for healthy aging therefore requires careful scientific scrutiny. Legitimate findings from environmental epidemiology and experimental neuroscience may be presented alongside claims concerning supplementation, but these represent different levels of evidence. A recommendation for preventive supplementation cannot be justified solely by observational associations or experimental findings.

The available evidence also suggests that the clinical relevance of lithium may depend on the biological context. Patients with mood disorders, individuals with cognitive impairment, and healthy populations differ in disease burden, baseline risk, and potential treatment responsiveness. It is therefore possible that a benefit observed in one population would not be reproduced in another. Future studies should address these differences explicitly rather than assuming a universal effect.

The present review has limitations. Its narrative methodology does not establish exhaustive literature coverage, and no formal meta-analysis or systematic risk-of-bias assessment was performed. The evidence is heterogeneous with respect to populations, formulations, exposure levels, and outcomes. Nevertheless, the integration of positive and negative findings provides a framework for interpreting the emerging literature without conflating established psychiatric treatment effects with unproven preventive applications.

Future research should prioritize rigorous clinical investigations with standardized exposure definitions, clinically meaningful endpoints, and long-term safety assessment. Cognitive outcomes and validated biological aging markers may provide useful intermediate information, but mortality and healthy lifespan remain distinct outcomes requiring appropriately designed studies.

5. Conclusion

Lithium has an established therapeutic role in psychiatry, and clinical evidence suggests that conventional treatment may be

associated with reduced mortality among patients with mood disorders. Environmental investigations have reported associations between trace lithium exposure and population mortality or dementia-related outcomes, while experimental research has identified biological mechanisms potentially relevant to neurodegeneration and aging. However, the evidence supporting microdose lithium supplementation as a longevity intervention remains insufficient. Recent clinical investigations have produced heterogeneous or inconclusive findings, and observational studies of biological aging have not consistently

demonstrated favorable associations. The discovery of altered endogenous lithium homeostasis in Alzheimer disease provides a compelling mechanistic hypothesis but does not establish clinical efficacy in humans. At present, no convincing randomized clinical evidence demonstrates that supplementation with approximately 1 mg of elemental lithium daily reduces all-cause mortality or extends human lifespan. Further investigation is scientifically justified, but routine preventive supplementation cannot be recommended on the basis of the available evidence.

Table 1: Classification of lithium exposure and relevance to mortality and longevity research

Exposure category	Characteristics	Principal research context	Evidence concerning longevity	References
Conventional therapeutic lithium	Pharmacological treatment with serum monitoring	Bipolar disorder and mood disorders	Mortality benefit suggested in psychiatric populations	[2–5,26]
Low-dose lithium	Exposure below conventional therapeutic targets	Cognitive impairment and neuropsychiatric research	No demonstrated lifespan extension	[2,13–20]
Microdose lithium	Very small administered quantities; terminology inconsistent	Exploratory cognitive and preventive research	No demonstrated mortality benefit	[2,12,18]
Environmental trace lithium	Naturally occurring lithium in water and food	Population epidemiology	Ecological mortality associations	[1,7–11,30–32]
Experimental lithium exposure	Controlled exposure in cellular and animal models	Neurodegeneration, autophagy, lifespan	Mechanistic and preclinical evidence	[7,21–24]

Note: These categories are descriptive and are not universally standardized. Lithium salt mass, elemental lithium content, serum concentration, and environmental concentration are distinct measurements.

Table 2: Principal clinical studies investigating conventional lithium treatment and mortality

Study	Design and population	Principal finding	Interpretation	Reference
Cipriani <i>et al.</i> , 2013	Meta-analysis of 48 randomized trials; 6,674 participants	Lower all-cause mortality versus placebo; OR 0.38 (95% CI 0.15–0.95)	Supports mortality benefit in mood disorders; limited mortality events	[3]
Chen <i>et al.</i> , 2023	Nationwide Taiwanese cohort; 25,787 patients with bipolar disorder	Lithium associated with lower adjusted mortality risks	Observational; potential confounding	[4]
Oliva <i>et al.</i> , 2025	Population-based cohort; 15,384 patients with bipolar disorder	Sustained exposure associated with lower mortality; HR 0.69 (95% CI 0.51–0.93)	Treatment continuity associated with improved survival	[5]
Mutz <i>et al.</i> , 2024	UK Biobank observational investigation	No significant association between lithium treatment duration and mortality	Does not support a duration-dependent longevity effect	[6]

Table 3: Environmental lithium exposure and mortality-related outcomes

Study	Setting	Outcome	Principal finding	Major limitation	Reference
Zarse <i>et al.</i> , 2011	Japanese municipalities	All-cause mortality	Inverse association with drinking-water lithium	Ecological design	[7]
Fajardo <i>et al.</i> , 2018	Texas counties	All-cause mortality	Inverse correlation; $r = -0.18$	Modest correlation; confounding	[8]
Kessing <i>et al.</i> , 2017	Denmark	Dementia incidence	Nonlinear association	Observational; geographic confounding	[9]
Duthie <i>et al.</i> , 2023	Scotland	Dementia incidence	No consistent protective association	Low exposure range and exposure uncertainty	[10]
Fraiha-Pegado <i>et al.</i> , 2024	Systematic review	Dementia incidence and mortality	Favorable associations in some studies	Heterogeneous observational evidence	[11]
Memon <i>et al.</i> , 2020	Meta-analysis of ecological studies	Population suicide mortality	Inverse association in pooled analysis	Ecological bias and heterogeneity	[30]
Eyre-Watt <i>et al.</i> , 2021	Systematic review and meta-analysis	Neuropsychiatric outcomes	Associations with selected population outcomes	Observational evidence	[31]
Fajardo <i>et al.</i> , 2018	Texas counties	Alzheimer disease mortality	Inverse ecological association	Disease-specific ecological outcome	[32]

Table 4: Clinical evidence concerning low-dose and microdose lithium in cognitive impairment

Study	Population	Exposure category	Follow-up	Main findings	Reference
Nunes <i>et al.</i> , 2013	Alzheimer disease	Microdose	15 months	Reported stabilization of cognitive performance	[12]
Forlenza <i>et al.</i> , 2011	Amnesic mild cognitive impairment	Low-dose	12 months	Favorable cognitive and biomarker findings	[13]
Forlenza <i>et al.</i> , 2019	Amnesic mild cognitive impairment	Low-dose	Long-term follow-up	Preliminary evidence of cognitive benefit	[14]
Matsunaga <i>et al.</i> , 2015	Meta-analysis of three randomized trials	Heterogeneous lithium exposures	Variable	Modest favorable pooled cognitive effect	[15]
Gildengers <i>et al.</i> , 2026	Mild cognitive impairment	Low-dose	24 months	None of six coprimary outcomes met the significance threshold	[16]
Pereira da Silva <i>et al.</i> , 2026	Meta-analysis of six randomized trials in Alzheimer dementia	Heterogeneous exposures	Variable	No consistent cognitive or functional benefit	[17]
Strawbridge <i>et al.</i> , 2023	Systematic review	Lower-dose interventions	Variable	Preliminary neuropsychiatric signals; heterogeneous evidence	[18]
Sabtiari <i>et al.</i> , 2025	Systematic review	Variable lithium exposures	Variable	Mixed cognitive findings	[19]
Neal <i>et al.</i> , 2024	Healthy adult volunteers	Lower-dose exposure	Short-term	Demonstrated feasibility of brain lithium detection	[20]

Table 5: Biological mechanisms potentially linking lithium to aging-related processes

Mechanism	Proposed biological relevance	Evidence category	Main limitation	References
GSK-3 inhibition	Regulation of neuronal signaling and protein phosphorylation	Experimental	Dose-specific clinical translation uncertain	[21,22]
Inositol monophosphatase inhibition	Regulation of intracellular signaling	Experimental	Human relevance at trace exposure uncertain	[23]
Autophagy	Intracellular protein clearance and homeostasis	Experimental	Clinical anti-aging effect unproven	[23]
NRF2 signaling	Cellular stress responses	Experimental lifespan models	Species-specific findings	[24]
Endogenous brain lithium homeostasis	Potential relationship with neurodegenerative pathology	Human tissue and animal models	No established preventive clinical intervention	[21]
Cognitive resilience	Possible modification of cognitive decline	Preliminary clinical	Inconsistent trial findings	[12–19]

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