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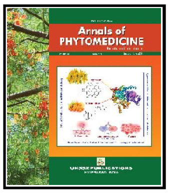

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Lithium as an essential micronutrient: Current evidence and future perspectives in human nutrition and health

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Abstract

Lithium, traditionally recognized for its psychiatric applications, is emerging as a potential essential micronutrient with significant implications for human health. This review synthesizes current evidence on lithium's biological roles, dietary sources, and health impacts. Beyond its established use in bipolar disorder, lithium demonstrates neuromodulatory, immunomodulatory, and neuroprotective properties even at microdose levels. It influences neurotransmitter systems, enhances neuroplasticity, and modulates immune responses by reducing inflammation and bolstering innate immunity. Lithium also exhibits neuroprotective effects through glycogen synthase kinase-3 (GSK-3) inhibition, antioxidant activity, and mitochondrial support, suggesting potential roles in preventing neurodegenerative disorders. Epidemiological studies link natural lithium exposure to improved mental health and reduced cardiovascular mortality, highlighting its broader public health relevance. Despite growing evidence, lithium's classification as an essential micronutrient remains unconfirmed due to methodological challenges. Understanding lithium's physiological significance could inform nutritional guidelines and therapeutic strategies for diverse conditions. This review underscores the need for further research to establish lithium's essentiality and optimize its health benefits.

1. Introduction

Lithium, a naturally occurring alkali metal, has a rich history in medicine dating back to the late 19th century when its salts were first used for treating gout and other ailments (Shorter, 2009). However, it was not until 1949 when John Cade published his landmark paper on lithium's efficacy in treating Mania that its psychiatric applications gained prominence (Cade and Malhi, 2007). For decades following this discovery, lithium has been primarily recognized for its therapeutic role in bipolar disorder, where it remains a gold standard treatment despite the introduction of numerous alternative medications (Malhi *et al.,* 2017). Its effectiveness in preventing both manic and depressive episodes, along with its unique anti-suicidal properties, has cemented lithium's place in psychiatric pharmacopeia (Cipriani *et al.,* 2013). While lithium's value in treating psychiatric conditions at pharmacological doses (typically 600-1200 mg/day) is well established, a paradigm shift has been occurring in scientific understanding of this element's biological significance (Szklarska and Rzymski, 2019). Emerging evidence suggests that lithium may play a more fundamental role in human physiology than previously recognized, functioning as an essential micronutrient rather than a pharmacological agent (Schrauzer, 2002). This reconceptualization has been driven by observations that lithium is ubiquitous in the food chain and present in all human tissues, characteristics typical of essential elements (Weinstein, 1976).

The notion that lithium might be essential for optimal health is supported by an expanding body of epidemiological evidence linking naturally occurring lithium in drinking water to numerous health outcomes (Kessing *et al.,* 2017). These associations span mental health parameters, including reduced suicide rates and aggressive behaviors, as well as physical health metrics such as cardiovascular mortality (Fajardo *et al.,* 2018). Such findings have led researchers to propose that environmental lithium exposure may contribute to public health at a population level, suggesting a biological requirement for this element (Memon *et al.,* 2020). Despite growing evidence, major health organizations have not officially classified lithium as an essential micronutrient (Buendía-Valverde *et al.,* 2024). This reflects both the relative newness of this research direction and the methodological challenges inherent in establishing essentiality for trace elements (Amdisen, 1990). To achieve such recognition, researchers must demonstrate that lithium performs specific biochemical functions that cannot be accomplished by other nutrients and that its absence results in reproducible physiological impairments.

The significance of understanding lithium's potential role as a micronutrient extends beyond scientific research. If lithium is indeed essential for human health, there are profound implications for nutritional guidelines, food fortification policies, and public health strategies (Schrauzer and Shrestha, 2010). Furthermore, this knowledge could inform new therapeutic approaches for conditions ranging from neurodegenerative disorders to mood disturbances, potentially at doses far lower than those used in conventional psychiatric practice (Marshall, 2015). As populations increasingly consume processed foods and purified water, which may contain less lithium than traditional diets and natural water sources,

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understanding the potential consequences of reduced lithium intake becomes increasingly relevant to public health (Kapusta *et al.,* 2011).

This review highlights the current state of evidence regarding lithium as a potential micronutrient, exploring its biological functions, dietary sources, health implications, and the challenges facing researchers in this emerging field. By synthesizing findings from diverse disciplines including biochemistry, epidemiology, neuroscience, and nutrition, we aim to provide a comprehensive overview of lithium's status as an element that may be essential for optimal human health and development.

2. Materials and Methods

Lithium, once primarily associated with psychiatric treatment, has garnered increasing interest in recent years as a potential essential micronutrient. Emerging evidence suggests that trace levels of lithium in the human diet may contribute to mental well-being, cognitive function, and overall longevity. As a result, lithium is being reconsidered within the broader context of nutritional science and public health.

To explore the evolving research landscape surrounding lithium in human nutrition and health, a bibliometric analysis was conducted using VOS viewer software. The analysis focused on co-occurrence mapping of keywords and clustering of research themes to identify prevailing scientific directions. Publication trends were also examined across five-year intervals from 2000 to 2025 to assess the growth in scholarly attention.

The network visualization revealed lithium as a central node in research clusters linked to human health, dietary micronutrients, and nutritional outcomes. Frequently co-occurring terms included "human," "micronutrients," "nutrition," and "health," indicating a clear shift in research focus toward the nutritional and preventive health roles of lithium. Additionally, the cumulative number of publications increased notably over the past two decades-from 13 articles between 2000-2004 to 43 articles between 2020-2025-highlighting a significant rise in academic interest and investigation.

The findings underscore a growing scientific recognition of lithium's potential importance in human nutrition. The increasing volume of publications and the emergence of human-focused dietary themes reflect a transition from pharmacological to physiological perspectives on lithium. This trend supports the need for further interdisciplinary studies to establish dietary reference values, identify natural food sources, and clarify lithium's mechanisms of action in human health. As research advances, lithium may be formally considered in future nutritional guidelines and public health policies.

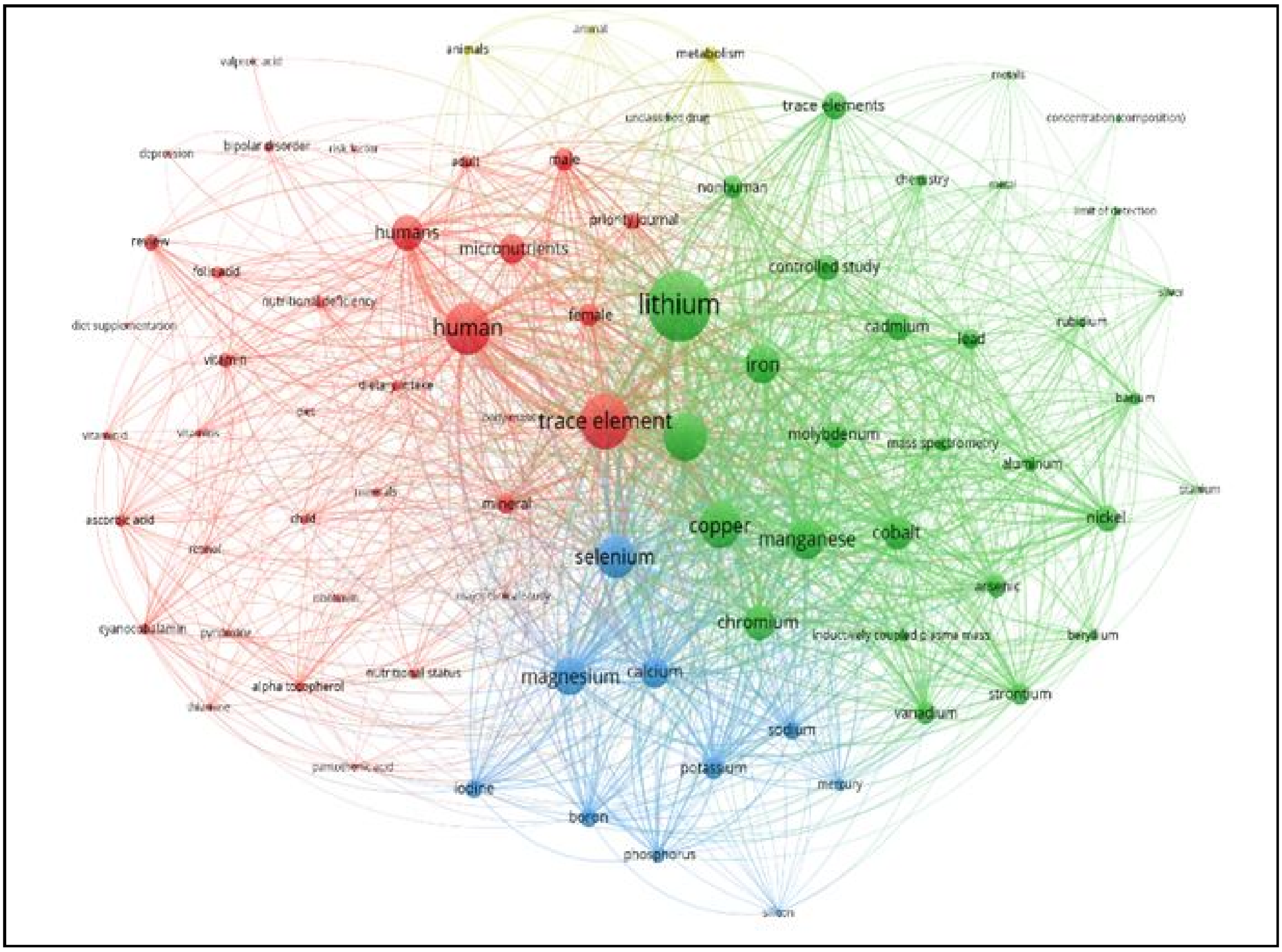

Figure 1: Bibliometric analysis (VOS viewer software).

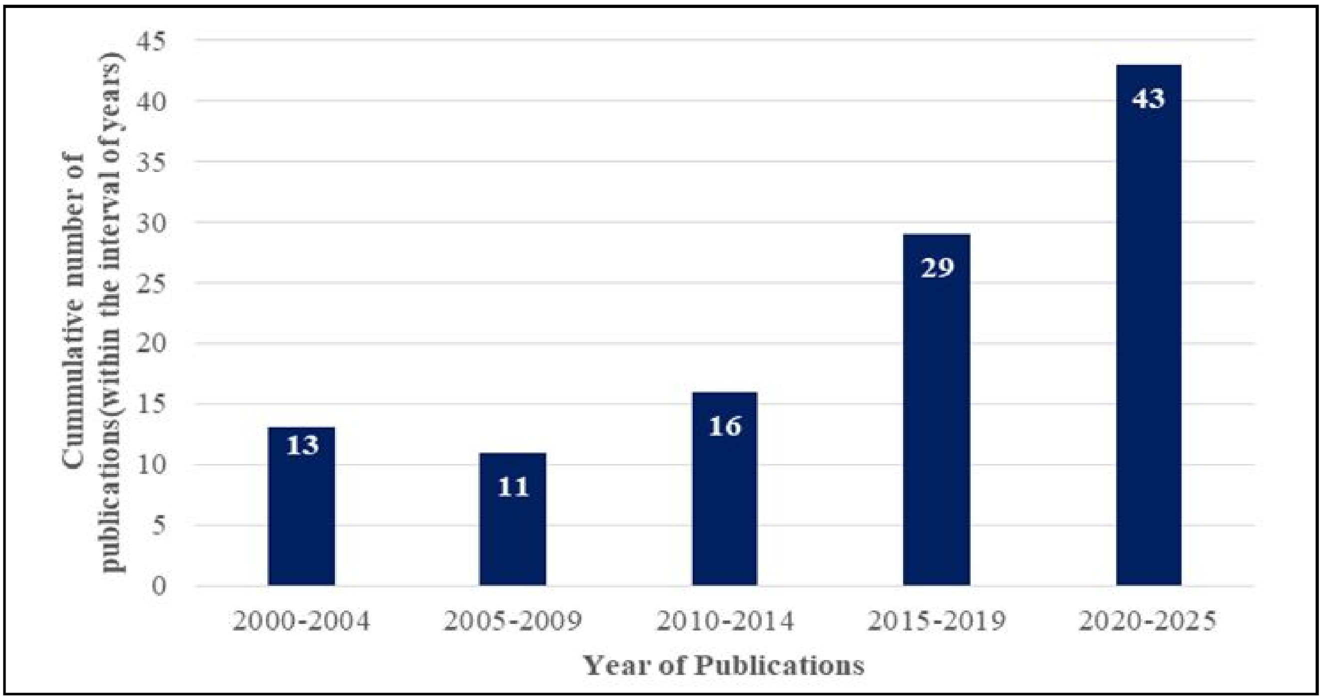

Figure 2: Cumulative number of publications on lithium in human nutrition and health (2000-2025).

3. Biological functions of lithium

3.1 Neuromodulation

Lithium exerts profound effects on neurotransmission systems through multiple mechanisms that collectively contribute to its therapeutic efficacy in psychiatric conditions and its potential role in normal brain function. At the neurotransmitter level, lithium modulates dopaminergic transmission by inhibiting dopamine-dependent behaviors and reducing dopamine receptor sensitivity, which may underlie its antimanic effects (Yatham and Malhi, 2003). This modulation appears dose-dependent, with even low concentrations affecting dopamine release and reuptake mechanisms in preclinical models (Malhi and Outhred, 2016). Similarly, lithium influences serotonergic pathways by enhancing serotonin synthesis and release while modifying receptor sensitivity, effects that have been linked to its antidepressant and anti-suicidal properties (Mohamadian *et al.,* 2023). The glutamatergic system is also significantly impacted, with lithium reducing glutamate-induced excitotoxicity through inhibition of N-methyl-D-aspartate (NMDA) receptor-mediated calcium influx and modulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor trafficking (Nonaka *et al.,* 1998). Beyond direct neurotransmitter effects, lithium modulates neuronal excitability through interactions with various ion channels. It competes with magnesium for binding sites on calcium channels, potentially altering calcium-dependent signaling cascades critical for neuronal function (Mørk *et al.,* 1992). Additionally, lithium influences sodium-potassium ATPase activity, which may contribute to its stabilizing effects on neuronal membrane potential (Pahwa *et al.,* 2023). These actions collectively dampen neuronal hyperexcitability, a process implicated in both mood disorders and epilepsy. Lithium's influence on second messenger systems represents one of its most well-characterized mechanisms of action. It inhibits inositol monophosphatase and inositol polyphosphate 1-phosphatase, leading to the depletion of free inositol and subsequent reduction in phosphatidylinositol signaling (Pahwa *et al.,* 2023). This "inositol depletion hypothesis" explains many of lithium's downstream effects on neuronal function and gene expression (Berridge, 2014). Additionally, lithium inhibits adenylate cyclase, reducing cAMP levels and modifying protein kinase A activity, which influences numerous cellular processes including neurotransmitter release and receptor sensitivity.

Perhaps most significantly, lithium promotes neuroplasticity through various pathways that enhance synaptic development and remodeling. It increases the expression of neurotrophic factors like BDNF (brain-derived neurotrophic factor), which supports neuronal survival, differentiation, and synaptic strengthening (Gideons *et al.,* 2017). Even at microdose levels below therapeutic concentrations, lithium may facilitate aspects of neuroplasticity, suggesting potential roles in normal brain development and maintenance (Taliyan and Ramagiri, 2016).

3.2 Immune system modulation

Lithium exerts significant modulatory effects on the immune system, influencing both innate and adaptive immune responses through direct actions on various white blood cell populations. Neutrophil function is notably enhanced by lithium treatment, with increased chemotaxis, phagocytosis, and superoxide production documented in both clinical and experimental studies (Focosi *et al.,* 2009). This effect may explain the occasional neutrophilia observed in patients receiving lithium therapy and suggests a potential role in bolstering innate immune defenses. Conversely, lithium appears to suppress certain T-lymphocyte functions, particularly T-helper cell activity, while enhancing natural killer cell cytotoxicity against target cells. These differential effects on lymphocyte subpopulations may contribute to lithium's complex immune modulatory profile

(Rapaport and Manji, 2001). The cytokine network, a critical component of immune regulation, undergoes significant remodeling in response to lithium exposure. Studies have consistently demonstrated lithium's capacity to reduce pro-inflammatory cytokine production, particularly interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) while enhancing anti-inflammatory mediators like IL-10 (Nassar and Azab, 2014). This anti-inflammatory bias may underlie lithium's therapeutic benefits in conditions characterized by neuro-inflammation, including certain psychiatric and neurodegenerative disorders.

Lithium also influences humoral immunity through effects on immunoglobulin production and B-cell function. Clinical studies have reported increased serum immunoglobulin concentrations in patients receiving long-term lithium therapy, suggesting enhanced B-cell activity (Sakrajda and Szczepankiewicz, 2021). This stimulatory effect appears to be direct, as in vitro studies demonstrate lithium-induced enhancement of B-cell proliferation and differentiation (Song *et al.,* 2017). The functional consequence of increased immunoglobulin production may include improved responses to certain pathogens, though the clinical significance of this effect at physiological lithium concentrations remains to be fully elucidated (McCarthy *et al.,* 2010). The inflammatory response, a coordinated physiological reaction to infection or tissue injury, is significantly modulated by lithium at multiple levels. By inhibiting Glycogen Synthase Kinase-3 beta (GSK-3β), lithium suppresses nuclear factor-κB (NF-κB) activation and subsequent inflammatory gene transcription in various cell types, including microglia and peripheral immune cells (Wang *et al.,* 2011). Additionally, lithium reduces prostaglandin synthesis through inhibition of phospholipase A2 activity, further contributing to its anti-inflammatory properties. At microdose levels comparable to those found in some drinking water sources, lithium still appears capable of subtly modulating inflammatory responses, suggesting that even environmental exposure may influence immune homeostasis.

3.3 Neuroprotection

Lithium's neuroprotective effects are mediated through multiple interconnected pathways, with inhibition of glycogen synthase kinase-3 (GSK-3) representing one of the most well-characterized mechanisms. At therapeutic concentrations, lithium directly inhibits GSK-3β activity through competition with magnesium ions at the enzyme's catalytic site, while also increasing inhibitory phosphorylation of the enzyme through activation of upstream kinases (Beaulieu and Caron, 2008). This inhibition yields numerous downstream effects that collectively promote neuronal survival, including reduced tau hyperphosphorylation and decreased β-amyloid production, both key pathological features in Alzheimer's disease (Noble *et al.,* 2005). Emerging evidence indicates that lithium can inhibit GSK-3 activity through both direct and indirect mechanisms, and this inhibition is considered a key contributor to its neuroprotective effects observed in various neurodegenerative and neuropsychiatric disease models (Sofola-Adesakin *et al.,* 2014). The promotion of neurotrophic factor expression represents another critical mechanism underlying lithium's neuroprotective properties. Chronic lithium treatment significantly increases the expression of BDNF in various brain regions, particularly the hippocampus and prefrontal cortex (Fukumoto *et al.,* 2001). Lithium exhibits significant antioxidant properties that contribute to its neuroprotective profile. By enhancing the expression and activity of antioxidant enzymes such as glutathione S-transferase, superoxide dismutase, and catalase, lithium reduces oxidative damage to cellular components (Machado-Vieira, 2018). Interestingly, studies suggest that even low-dose lithium supplementation can enhance antioxidant defenses, implying that dietary lithium may contribute to protection against oxidative damage (Castillo-Quan *et al.,* 2016). The anti-apoptotic effects of lithium involve multiple pathways that collectively promote neuronal survival under stress conditions. Lithium inhibits the intrinsic apoptotic pathway by preventing the release of cytochrome c from mitochondria and subsequent activation of caspase-3, a key executioner of caspase in programmed cell death (Rowe and Chuang, 2004). Lithium exerts significant influences on mitochondrial function, enhancing cellular energy production and resilience. It promotes mitochondrial biogenesis through activation of the Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) pathway, leading to increased mitochondrial mass and improved energy metabolism (Valvassori *et al.,* 2010). Emerging evidence suggests that lithium's effects on mitochondrial function may occur even at concentrations achievable through dietary intake, potentially contributing to its proposed role as a micronutrient.

4. Dietary sources and intake

4.1 Food sources

Lithium is naturally present in varying concentrations across a wide range of food items, with plant-based foods generally containing higher amounts than animal products. Nuts and seeds represent particularly rich sources, with Brazil nuts containing 8.6 μg/g, walnuts 6.8 μg/g, and pistachios 3.7 μg/g of dry weight, making them among the most lithium-dense foods in typical diets (González-Weller *et al.,* 2013). Legumes also contribute significantly to dietary lithium intake, with lentils and kidney beans containing approximately 4.9 μg/g and 3.8 μg/g, respectively, likely due to their ability to concentrate minerals from soil. Cereal grains demonstrate moderate lithium content, with oats containing approximately 2.3 μg/g and wheat products ranging from 1.2-2.7 μg/g, though processing methods may significantly affect final concentrations (Franzaring *et al.,* 2016). The lithium content in plant foods appears highly dependent on soil composition, agricultural practices, and environmental factors, leading to substantial geographical variation in content even within the same food types (Mukherjee). Animal-based foods generally contain lower lithium concentrations compared to plant sources, reflecting lithium's limited role in animal physiology and its non-bioaccumulative nature. Seafood represents the richest animal source, with certain fish and shellfish containing between 0.5-3.0 μg/g, likely reflecting the higher lithium content in ocean waters compared to freshwater (Schrauzer, 2002). Dairy products contain minimal lithium, typically less than 0.5 μg/g, while eggs contain approximately 0.2-0.6 μg/g, with concentrations influenced by the lithium content in animal feed and water sources. Meat products generally contain the lowest lithium concentrations among food categories, with levels typically below 0.5 μg/g across beef, pork, and poultry, though organ meats may contain slightly higher amounts (Sobolev *et al.,* 2019). Vegetables and fruits demonstrate considerable variation in lithium content, with certain varieties emerging as relatively important dietary sources. Among vegetables, spinach and tomatoes show notably higher lithium concentrations (1.8-2.3 μg/g and 1.5-2.0 μg/g, respectively), compared to other commonly consumed varieties. Root vegetables generally contain moderate amounts, with potatoes averaging 0.9 µg/g and carrots approximately 0.7 µg/g, concentrations that reflect soil mineral content where they were grown (Iordache *et al.,* 2024).

Regional variations in food lithium content present a significant challenge in estimating typical dietary intake across populations. Soil lithium content varies dramatically across geographical regions, ranging from less than 1 ppm in certain areas to over 100 ppm in others, directly influencing the mineral composition of locally grown foods (Kszosand Stewart, 2003). Foods grown in regions with lithium-rich soil, such as parts of northern Chile, Argentina, and certain areas of the western United States, consistently show higher lithium concentrations across all plant food categories (Figueroa *et al.,* 2012). Agricultural practices further influence food lithium content, with irrigation water source, fertilizer use, and soil amendments all affecting final concentrations (Schrauzer, 2002). These factors collectively contribute to the challenges in establishing standardized estimates of lithium intake from food sources alone, highlighting the importance of considering local geological and agricultural conditions when assessing nutritional lithium status.

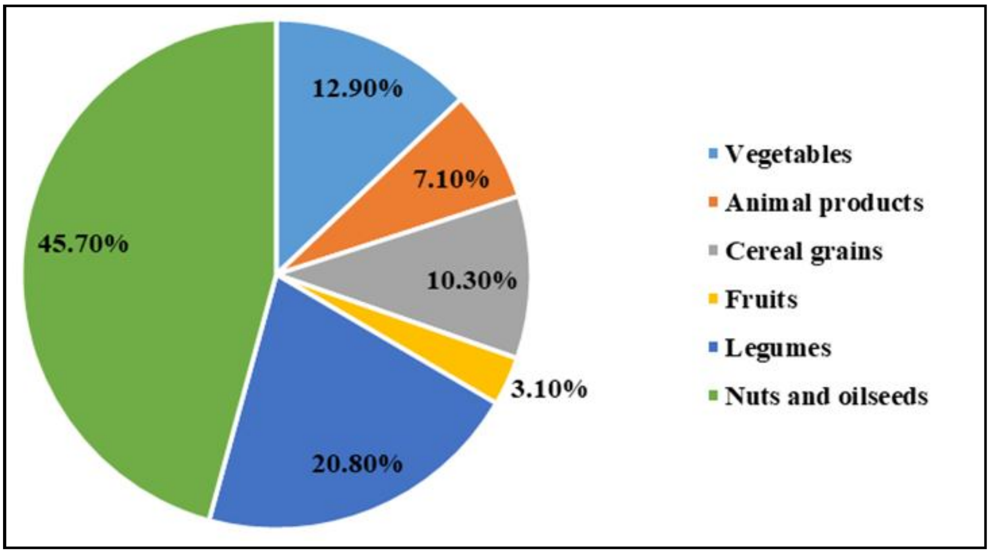

Figure 3: Dietary sources of lithium (in percentage).

4.2 Water sources

Tap water represents a significant source of dietary lithium in many regions, with concentrations varying dramatically based on geological and hydrological factors. Municipal water supplies worldwide show lithium concentrations ranging from undetectable levels (<0.001 mg/l) to extraordinarily high values exceeding 1 mg/l in certain geological regions, particularly those near mineral deposits or thermal springs (Kszos and Stewart, 2003). Studies mapping water lithium content across different countries have revealed striking regional variations, with mean concentrations of 0.0105 mg/l reported across 24 regions in Japan (Ohgami *et al.,* 2009), 0.0113 mg/l across 47 prefectures in Portugal (Kapusta *et al.,* 2011), and dramatically higher values averaging 0.125 mg/l in northern Chile's Atacama region (Figueroa *et al.,* 2012). These geographical differences in water lithium content have been associated with varying health outcomes in epidemiological studies, particularly regarding mental health parameters including suicide rates and violent behavior (Liaugaudaite *et al.,* 2017). Commercial mineral waters exhibit considerable variation in lithium content, providing another potential dietary source of this element. Analysis of bottled mineral waters from various European sources revealed lithium concentrations ranging from undetectable to 5.2 mg/l, with a median value of approximately 0.05 mg/l, significantly higher than typical tap water values (Demetriades *et al.,* 2010). Waters specifically marketed for their mineral content often contain higher lithium levels, with certain brands from lithium-rich springs containing 1-3 mg/l, potentially providing a significant contribution to daily intake for regular consumers (González-Weller *et al.,* 2013) The lithium content in bottled water typically reflects the geological characteristics of the source aquifer, with thermal and mineral springs generally yielding higher concentrations than shallow aquifers or surface water sources. Geological factors exert the primary influence on water lithium content, with several key determinants identified across hydrological studies. Lithium concentrations are typically highest in waters that have contact with igneous rocks, particularly granites and certain volcanic formations, due to the weathering of lithium-containing minerals such as spodumene, lepidolite, and lithium micas (Kabata-Pendias and Szteke, 2015). Areas with lithium-bearing clay deposits, especially those formed through historical hydrothermal activity, also frequently demonstrate elevated water lithium levels. Groundwater generally contains higher lithium concentrations than surface water due to extended rock-water interaction time, with deep aquifers and thermal springs typically showing the highest values (Ann Munk *et al.,* 2025). Additionally, arid regions may develop elevated lithium concentrations in groundwater due to evaporative concentration effects, as observed in certain desert basins where lithium-rich brines have formed (Kesler *et al.,* 2012). These geological determinants create distinct "lithium provinces" worldwide, where populations may be exposed to significantly different levels of this element through their water supply.

Water treatment processes can significantly impact the lithium content of drinking water, with implications for dietary intake and public health. Conventional treatment methods including coagulation, sedimentation, and sand filtration have minimal effect on lithium concentrations, as lithium predominantly exists in water as free ions rather than particulate-bound forms (Jin *et al.,* 2021). Similarly, disinfection processes including chlorination and UV treatment do not appreciably alter lithium levels (Pompili *et al.,* 2015). However, advanced treatment technologies increasingly employed in municipal water systems and home filtration devices can substantially reduce lithium content; ion exchange systems may remove 30-90% of lithium depending on resin type and contact time, while reverse osmosis typically eliminates 90-98% of this element alongside other minerals (Xu *et al.,* 2024). The proliferation of household water purification systems and bottled water consumption potentially reduces lithium intake in populations that would otherwise receive moderate amounts through unfiltered tap water (Ohgami *et al.,* 2009). This trend raises questions about potential nutritional implications if lithium indeed functions as an essential micronutrient, particularly in regions where water represents the primary source of dietary lithium.

4.3 Recommended intake

Current guidelines regarding lithium intake remain provisional, reflecting the element's ambiguous status between established pharmaceutical agents and potential micronutrients. The United States Environmental Protection Agency established a provisional Recommended Daily Allowance (RDA) for lithium of 1000 ìg/day for a 70 kg adult, though this recommendation lacks formal adoption by major nutritional organizations (Schrauzer, 2002). This provisional value was derived from estimated typical intake levels rather than from experimental determination of physiological requirements, highlighting the preliminary nature of current recommendations (Vita *et al.,* 2015). The World Health Organization has not established specific dietary guidelines for lithium, though its joint expert committee with the Food and Agriculture Organization recognized lithium as a trace element potentially essential to human health (FAO, 2004). Some researchers have suggested that optimal intake may range between 650-3100 µg/day based on epidemiological data examining health outcomes in populations exposed to different environmental lithium levels (Fadaei, 2023).

Epidemiological evidence provides valuable insights into potential optimal lithium intake levels through studies examining health parameters across populations with varying environmental exposure. Investigations of drinking water lithium content and mental health outcomes have consistently identified inverse associations between lithium exposure and suicide rates across diverse geographical regions including Japan, Austria, Greece, Italy, Lithuania, and the United States (Liaugaudaite *et al.,* 2017). These associations appear strongest when comparing regions with water lithium concentrations below 30 µg/l versus those above this threshold, suggesting potential protective effects beginning at relatively low exposure levels (Fajardo *et al.,* 2018). Similarly, studies examining violent crime rates, dementia incidence, and all-cause mortality have identified potential threshold effects, with benefits observed at estimated total lithium intakes of approximately 1000 µg/day (range 650-3100 µg/day) from combined dietary sources (Kessing *et al.,* 2017). While these epidemiological associations cannot establish causality, they provide preliminary evidence supporting the provisional intake recommendations proposed by some researchers.

Age and gender considerations may influence optimal lithium intake, though research specifically addressing demographic variations remains limited. Developmental periods may require different lithium levels, with animal studies suggesting particular importance during early brain development and potentially in adolescence when significant neural pruning and refinement occur (Makoukji *et al.,* 2012). Prenatal lithium exposure through maternal diet appears to influence offspring neurodevelopment in animal models, suggesting potential critical periods when adequate intake may be especially important (Zarse *et al.,* 2011). Gender differences in lithium pharmacokinetics have been observed in clinical studies, with females typically showing higher plasma concentrations than males given equivalent weight-adjusted doses, potentially due to differences in total body water, glomerular filtration rate, and hormonal influences on drug metabolism (Sproule *et al.,* 2000). However, these pharmacokinetic differences have been primarily studied at therapeutic doses, and their relevance to trace dietary intake remains speculative (Marshall, 2015). Some evidence suggests postmenopausal women may particularly benefit from adequate lithium intake due to its potential effects on bone metabolism and density, though targeted research examining gender-specific requirements is lacking.

Bioavailability factors significantly influence the absorption and utilization of dietary lithium, potentially affecting the relationship between intake and physiological effects as mentioned in Table 1. Lithium is primarily absorbed in the small intestine, with approximately 70-100% bioavailability from water sources and somewhat lower absorption from food matrices (80-90%), depending on specific dietary components (Schrauzer, 2002). Absorption appears to occur primarily through sodium channels, with high dietary sodium potentially reducing lithium uptake through competitive inhibition. Conversely, lithium absorption may be enhanced in low-sodium diets, potentially increasing the effective dose from equivalent intake levels (Haddad *et al.,* 2021). Certain dietary components including caffeine and theophylline may increase lithium clearance, potentially reducing retention from equivalent intake. The chemical form of lithium appears to influence bioavailability, with organic complexes potentially offering different absorption and distribution profiles compared to inorganic salts, though research specifically comparing lithium forms at nutritional doses remains limited (Jefferson and Greist, 1978). These bioavailability considerations highlight the complexity of establishing universal intake recommendations without accounting for dietary patterns that may significantly alter lithium retention and utilization.

Table 1: Bioavailability factors

Factor	Effect on lithium bioavailability	References
Water sources	70-100% absorption	Schrauzer, 2002
Food matrices	80-90% absorption	Schrauzer, 2002
High dietary sodium	Reduced absorption	Haddad *et al.,* 2002
Low-sodium diet	Enhanced absorption	Sproule *et al.,* 2000
Caffeine/theophylline	Increased clearance	Jefferson *et al.,* 1982

5. Health implications

5.1 Mental health

Lithium's effects on mood regulation at trace doses have garnered increasing scientific attention, with evidence suggesting that even concentrations well below therapeutic levels may influence neurochemical processes relevant to mood stabilization. Animal studies demonstrate that microdose lithium exposure (approximately 20-400 μg/kg/day) modulates monoaminergic neurotransmission, particularly serotonergic and dopaminergic systems, without producing the side effects associated with pharmacological doses (Zarse *et al.,* 2011). These effects appear mediated through similar molecular mechanisms as therapeutic lithium, including inhibition of glycogen synthase kinase-3β (GSK-3β) and modulation of inositol monophosphatase, though with more subtle neurobiological impacts (Matsunaga *et al.,* 2015). Human observational studies provide additional support, with individuals living in regions with moderately elevated water lithium (30-100 μg/l) demonstrating lower rates of mood disorders and related mental health hospitalizations compared to regions with minimal lithium exposure (Kessing *et al.,* 2017). While these associations cannot establish causality, the dose-response relationship observed across multiple independent investigations suggests potential physiological effects at environmentally relevant exposure levels (Enderle *et al.,* 2020). Epidemiological studies examining the relationship between environmental lithium exposure and suicide rates have yielded remarkably consistent findings across diverse geographical regions and populations. Pioneering research in Texas identified a significant inverse association between tap water lithium concentrations and suicide rates across 27 counties, with each 100 μg/l increase in water lithium associated with an 8.7% reduction in suicide mortality (Fadaei, 2023). Subsequent investigations replicated these findings in Japan, Austria, Greece, Italy, and Lithuania all demonstrating significant negative correlations between environmental lithium exposure and suicide rates after controlling for socioeconomic confounders. Meta-analyses of these ecological studies suggest that regions with water lithium exceeding 30 μg/l demonstrate approximately 15-20% lower suicide rates compared to regions with minimal lithium (<1 μg/l), with the relationship appearing particularly pronounced for violent suicide methods (Barjasteh-Askari *et al.,* 2020). These population-level associations align with lithium's well-established anti-suicidal properties at therapeutic doses, suggesting potential continuity of effect across a broad concentration spectrum.

The relationship between environmental lithium exposure and aggressive or violent behavior has been examined in several ecological studies, yielding intriguing though preliminary findings. Research across 27 Texas counties found significant inverse correlations between tap water lithium levels and rates of homicide, rape, and assault, with each 100 μg/l increase in lithium associated with an approximately 13% reduction in violent crime rates after controlling for population density and socioeconomic factors (Schrauzer and Shrestha, 2010). Experimental evidence provides partial mechanistic support for these observations, as animal studies demonstrate that low-dose lithium supplementation reduces aggressive behaviors and increases social interaction through modulation of serotonergic neurotransmission and inhibition of GSK-3β activity (O'Donnell and Gould, 2007). These findings align with lithium's documented effects on impulsivity and aggression at therapeutic doses in psychiatric populations, suggesting a potential continuum of effect across a range of concentrations. Lithium appears to influence physiological stress response systems at both pharmacological and nutritional concentrations, potentially contributing to its mood-stabilizing properties. Research demonstrates that chronic lithium exposure modulates hypothalamic-pituitary-adrenal (HPA) axis activity, reducing stress-induced cortisol secretion and promoting normalization of feedback inhibition mechanisms often disrupted in mood disorders (Watson *et al.,* 2007). This effect appears partially mediated through lithium's inhibition of GSK-3β, which influences glucocorticoid receptor sensitivity and subsequent negative feedback regulation. Animal studies suggest that even low-dose lithium supplementation (400 μg/kg/day) attenuates behavioral and neuroendocrine responses to stress, enhancing resilience to chronic unpredictable stressors (Khan *et al.,* 2015). These effects on stress response systems may be particularly relevant in contemporary populations exposed to chronic psychosocial stressors, potentially explaining some of the epidemiological associations between environmental lithium and mental health outcomes (Malhi and Outhred, 2016).

Emerging research indicates that trace lithium exposure may help alleviate anxiety symptoms, as shown in animal models. These effects appear mediated through lithium's modulation of several neurotransmitter systems implicated in anxiety, including enhanced GABAergic transmission, normalized glutamatergic signaling, and reduced noradrenergic hyperactivity (Machado-Vieira *et al.,* 2009). Human studies provide indirect support through ecological analyses demonstrating lower anxiety disorder prevalence in regions with moderately elevated water lithium concentrations (30-100 μg/l) compared to areas with minimal exposure (Kessing *et al.,* 2017). Given the high prevalence of anxiety disorders worldwide and the limitations of current treatment approaches, further investigation of lithium's potential anxiolytic effects at nutritional doses represents an important research direction.

5.2 Neuroprotection and cognitive function

Lithium demonstrates significant neuroprotective potential against neurodegenerative diseases, with evidence from both experimental models and epidemiological studies suggesting benefits across multiple pathological processes. In Alzheimer's disease models, lithium administration inhibits both the production and aggregation of β-amyloid through GSK-3β inhibition and regulation of amyloid precursor protein processing (Rockenstein *et al.,* 2007). Additionally, lithium reduces tau hyperphosphorylation and subsequent neurofibrillary tangle formation, another key pathological feature of Alzheimer's disease, through direct inhibition of tau kinases. In Parkinson's disease models, lithium demonstrates protection against dopaminergic neuron degeneration through multiple mechanisms including autophagy enhancement, α-synuclein clearance, and reduction of oxidative stress-induced apoptosis (Wang *et al.,* 2024). Similarly, studies in amyotrophic lateral sclerosis (ALS) models indicate that lithium treatment prolongs survival and preserves motor function through enhanced autophagy, reduced excitotoxicity, and promotion of mitochondrial function (Fornai *et al.,* 2008). Importantly, these neuroprotective effects appear present even at subtherapeutic doses in many experimental paradigms, suggesting potential benefits at nutritionally relevant concentrations. Lithium influences cognitive function through effects on synaptic plasticity, neurogenesis, and neural network activity. In animals, chronic lithium treatment enhances long-term potentiation-key to learning and memory *via* NMDA receptor modulation and downstream signaling (Nocjar *et al.,* 2007). It also promotes hippocampal neurogenesis by increasing neural progenitor proliferation and neuron survival through BDNF upregulation and GSK-3β inhibition. Human studies show that low-dose lithium (150-600 mg/day) improves executive function, memory, and attention (Aprahamian *et al.,* 2014). Population studies link moderately elevated lithium in drinking water (30-80 μg/l) to reduced cognitive decline and a 17-22% lower dementia incidence (Fajardo *et al.,* 2018). While not causal, these findings align with lithium's known neuroplastic and cellular resilience effects.

Emerging research highlights lithium's role in brain development, with lasting impacts on mental health. Animal studies show that maternal lithium deficiency leads to impaired neurogenesis, abnormal neuronal migration, cognitive deficits, and anxiety-like behavior in offspring (Schrauzer and de Vroey, 1994). Adequate developmental lithium promotes normal neuronal differentiation, synaptic pruning, and myelination via pathways like Wnt/β-catenin and Notch (Quiroz *et al.,* 2010). These effects are most pronounced during rapid brain development. Limited human data suggest regional lithium exposure may influence academic and behavioral outcomes, though confounders make interpretation cautious (Viguera *et al.,* 2001). Lithium may protect against age-related cognitive decline by targeting key brain aging mechanisms. Chronic low-dose lithium reduces oxidative damage by boosting antioxidant systems like glutathione, superoxide dismutase, and catalase. It also limits neuroinflammation by inhibiting microglial activation and lowering pro-inflammatory cytokines (Nassar and Azab, 2014). Human studies support these effects; a randomized trial showed improved memory and attention in older adults with mild cognitive impairment after 15 months of low-dose lithium (Nunes, 2018) and a cohort study linked higher lithium intake to slower cognitive decline over 10 years.

Lithium also significantly reduces neuroinflammation, a key factor in neuropsychiatric and neurodegenerative diseases. It suppresses NF-κB signaling and lowers cytokines like IL-1α, TNF-α, and IL-6 while promoting a shift in microglia from a pro-inflammatory to a neuroprotective state (Nassar and Azab, 2014). Even microdoses (20-100 μg/kg/day) reduce neuroinflammation in models of Alzheimer's, brain injury, and stroke (Forlenza *et al.,* 2014). Though human trials are limited, regional lithium exposure has been linked to a lower prevalence of neuroinflammatory conditions (Damri and Agam, 2024). These anti-inflammatory effects may underlie lithium's broader health benefits.

5.3 Cardiovascular health

Lithium appears to influence vascular function through multiple mechanisms affecting endothelial cell biology and vascular tone regulation. *In vitro* studies demonstrate that lithium treatment enhances nitric oxide synthase activity in endothelial cells, promoting vasodilation and improving microcirculation through increased nitric oxide production (Bosche *et al.,*2016). Additionally, lithium reduces endothelial inflammation and oxidative stress by inhibiting NADPH oxidase activity and subsequent reactive oxygen species generation, potentially protecting against atherosclerotic processes (Lv *et al.,* 2019). Human epidemiological studies offer preliminary support for these experimental findings, with ecological analyses identifying inverse associations between lithium levels in drinking water and hypertension prevalence after controlling for socioeconomic and lifestyle factors. Lithium exerts notable effects on cardiac rhythm regulation through modulation of ion channel function and autonomic nervous system activity. Research demonstrates that lithium influences calcium channel dynamics in cardiac tissue, potentially stabilizing electrical conduction and reducing arrhythmogenic triggers (El-Mallakh, 1988). Animal models have demonstrated that chronic low-dose lithium treatment reduces the incidence and severity of experimentally induced arrhythmias, potentially through these autonomic and ion channel effects (Ishii and Terao, 2018). In clinical populations receiving therapeutic lithium, reduced incidence of certain arrhythmias has been observed compared to matched controls, though distinguishing direct cardiac effects from indirect benefits via mood stabilization remains challenging (Bosche *et al.,* 2016). Limited evidence suggests that even environmental lithium exposure may influence cardiac rhythm parameters, with ecological studies identifying associations between regional lithium levels and reduced sudden cardiac death rates, though such findings require cautious interpretation given potential confounders (Zarse *et al.,* 2011).

Emerging evidence suggests lithium may exert protective effects against atherosclerosis through multiple mechanisms targeting key pathological processes in plaque formation and progression. Laboratory studies demonstrate that lithium inhibits vascular smooth muscle cell proliferation and migration, critical events in atherosclerotic plaque development, through GSK-3β inhibition, and subsequent effects on cell cycle regulation (Munteanu *et al.,* 2022). In animal models, chronic lithium treatment reduces atherosclerotic lesion size and complexity in hyperlipidemic conditions, with effects observed even at doses below the therapeutic range (Bergmann *et al.,* 2007). Limited human data provides indirect support, with observational studies in psychiatric populations suggesting reduced atherosclerotic burden in long-term lithium users compared to those receiving other psychotropic medications, even after controlling for cardiovascular risk factors.

Lithium influences lipid metabolism through several pathways potentially relevant to cardiovascular risk profiles. Research demonstrates that lithium modulates lipid biosynthesis and transport through effects on sterol regulatory element-binding proteins (SREBPs) and peroxisome proliferator-activated receptors (PPARs), key transcription factors regulating genes involved in lipid homeostasis (Can *et al.,* 2014). In preclinical models, lithium treatment has been associated with improved lipid profiles, including reduced total cholesterol, lower low-density lipoprotein (LDL), and increased high-density lipoprotein (HDL) concentrations through these transcriptional effects (de Sousa *et al.,* 2011). Human studies present mixed findings, with some indicating favorable lipid profile changes among psychiatric patients receiving long-term lithium therapy, while others report neutral effects (Baptista *et al.,* 1995). Limited evidence from population studies suggests that regions with moderately elevated environmental lithium exposure demonstrate a lower prevalence of dyslipidemia compared to areas with minimal lithium levels, though such ecological associations require cautious interpretation given numerous potential confounders.

5.4 Metabolic effects

Lithium impacts glucose regulation through multiple mechanisms affecting insulin signaling and pancreatic β-cell function. Research demonstrates that lithium enhances insulin receptor substrate (IRS) phosphorylation and subsequent PI3K/Akt pathway activation, key steps in insulin signal transduction that promote glucose uptake in peripheral tissues (Baptista *et al.,* 1995). Additionally, lithium inhibits GSK-3β, a negative regulator of insulin signaling that is hyperactive in insulin-resistant states, potentially improving cellular insulin sensitivity through this canonical pathway (Pasquali *et al.,* 2010). Studies in pancreatic tissue indicate that lithium promotes β-cell survival and insulin secretion through CREB pathway activation and subsequent anti-apoptotic and pro-proliferative effects (Liang *et al.,* 2008). Animal models provide supporting evidence, with chronic low-dose lithium treatment improving glucose tolerance and insulin sensitivity in diabetic models through these molecular mechanisms (Lazarus, 2013). Findings from human studies remain inconclusive; while some investigations have demonstrated improved glycemic control in patients with psychiatric disorders receiving therapeutic lithium (Rybakowski, 2020), others have reported neutral or adverse effects. These discrepancies may be attributed to dose-dependent factors or individual variations in metabolic response. Lithium demonstrates significant effects on bone health through multiple mechanisms influencing mineral metabolism and skeletal remodeling. Laboratory studies reveal that lithium enhances osteoblast proliferation and differentiation while inhibiting osteoclast activity through modulation of the Wnt/β-catenin signaling pathway, a key regulator of bone formation (Clément-Lacroix *et al.,* 2005). By inhibiting GSK-3β, lithium prevents β-catenin phosphorylation and subsequent degradation, promoting its nuclear translocation and activation of target genes involved in osteogenesis. Lithium interacts with thyroid hormone function through multiple mechanisms affecting both hormone synthesis and receptor activity. Research demonstrates that lithium inhibits thyroid hormone release from the thyroid gland by disrupting iodine uptake and thyroglobulin processing, potentially leading to reduced circulating thyroid hormone levels with chronic exposure (Lazarus, 2009). Additionally, lithium influences deiodinase enzymes that convert thyroxine (T4) to the more active triiodothyronine (T3), affecting peripheral hormone activation and metabolism (Kibirige *et al.,* 2013). At the cellular level, lithium modulates thyroid hormone receptor sensitivity through effects on post-translational modifications and cofactor recruitment, potentially altering tissue responsiveness to available hormones (Kibirige *et al.,* 2013). These effects appear dose-dependent, with therapeutic concentrations frequently associated with subclinical hypothyroidism, while the impact of trace dietary levels remains less clearly established (McKnight *et al.,* 2017). Limited evidence suggests potential beneficial effects of low-dose lithium in certain thyroid disorders, with case reports and small studies indicating possible benefits in Graves' disease through moderation of autoimmune processes, though larger controlled trials are lacking (Fairbrother *et al.,* 2019).

Emerging evidence suggests lithium may influence weight regulation and energy metabolism through effects on hypothalamic circuits and peripheral metabolic tissues. Research demonstrates that lithium modulates hypothalamic neuropeptide expression, particularly affecting orexigenic and anorexigenic signals that regulate appetite and satiety (Baptista *et al.,* 1995). In peripheral tissues, lithium influences substrate metabolism by promoting glucose oxidation while modulating lipid utilization through effects on key metabolic enzymes including pyruvate dehydrogenase and acetyl-CoA carboxylase (Bosetti *et al.,* 2002). Animal studies provide supporting evidence, with low-dose lithium supplementation preventing diet-induced obesity in some models through these central and peripheral mechanisms (Zarse *et al.,* 2011). Human data offers mixed findings, with therapeutic lithium commonly associated with modest weight gain in psychiatric populations, while limited evidence suggests potential metabolic benefits at lower environmental exposure levels, though such ecological associations require cautious interpretation.

Table 2: Health implications of lithium: Research evidence

Health domain	Specific effect	Research evidence	References
Mental health	Mood regulation	Trace doses of lithium demonstrate mood-stabilizing effects even in non-clinical populations.	Schrauzer and Shrestha, 1990
	Suicide prevention	Inverse correlation between lithium levels in drinking water and suicide rates across 27 Texas counties.	Blüml *et al.,* 2013
	Aggression and violence	Communities with higher lithium in water supply show statistically lower crime rates and aggressive behavior.	Malhi *et al.,* 2017; Schrauzer and Shrestha, 2010
	Stress response	Lithium modulates HPA axis function and improves stress resilience *via* GSK-3β inhibition.	Malhi *et al.,* 2017
	Anxiety disorders	Low-dose lithium may reduce anxiety symptoms through serotonergic system modulation.	Shaldubina *et al.,* 2001
Neuroprotection and cognitive function	Neurodegenerative diseases	Lithium treatment shown to reduce phosphorylated tau protein and β-amyloid production in Alzheimer's models.	Forlenza *et al.,* 2014
	Cognitive enhancement	Chronic low-dose lithium improves spatial memory and cognitive performance in animal models.	Nocjar *et al.,* 2007
	Brain development	Lithium influences neurogenesis and synaptogenesis during critical developmental windows.	Kim *et al.,* 2004
	Brain aging	Long-term lithium treatment associated with increased brain gray matter volume and preserved cognition in older adults.	Monkul *et al.,* 2007
	Neuro-inflammation	Lithium reduces microglial activation and pro-inflammatory cytokine production.	Fornai *et al.,* 2008
Cardiovascular health	Vascular function	Lithium improves endothelial function *via* nitric oxide synthase activation.	Rybakowski, 2020

Metabolic effects	Cardiac rhythm	Therapeutic levels can stabilize cardiac membrane potential, potentially reducing arrhythmia risk.	Belmaker *et al.*, 1979
	Atherosclerosis	Lithium treatment reduces atherosclerotic plaque formation in ApoE-deficient mice.	Choi *et al.*, 2019
	Lipid metabolism	Long-term lithium therapy may alter cholesterol metabolism through GSK-3β inhibition.	Tabata *et al.* (2008),
	Glucose regulation	Lithium enhances insulin sensitivity through multiple molecular pathways.	Henriksen and Dokken, 2006
	Bone health	Lithium promotes osteoblast differentiation and inhibits osteoclast activity.	Clément-Lacroix *et al.*, 2005
	Thyroid function	Lithium inhibits thyroid hormone release and can induce hypothyroidism in some patients.	Lazarus, 2013
	Weight regulation	Complex effects on appetite and metabolism, often associated with moderate weight gain in clinical populations.	McKnight *et al.*, 2017

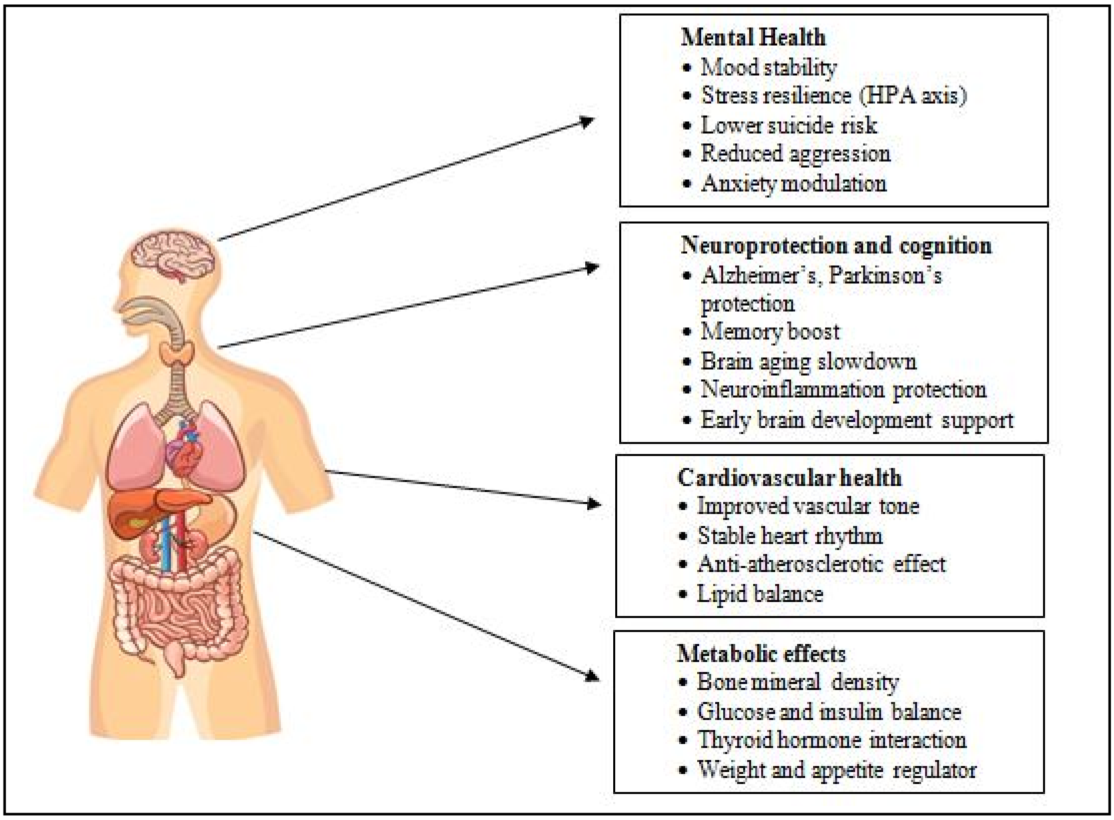

Figure 4: Systemic health effects of dietary lithium: From brain to body.

6. Challenges and future directions

6.1 Data limitations

Research on lithium as a micronutrient faces significant methodological challenges, primarily due to difficulties in conducting controlled studies with trace amounts of lithium in human populations (Szklarska and Rzymski, 2019). The field struggles with establishing clear dose-response relationships, as effects appear to follow a non-linear pattern with potential benefits at very low doses that differ substantially from therapeutic psychiatric doses (Kessing *et al.*, 2017). Cross-sectional studies have provided valuable epidemiological data linking environmental lithium exposure to mental health outcomes, but causality remains difficult to establish without more longitudinal investigations (Fajardo *et al.*, 2018). Meta-analyses have been hampered by heterogeneity in measurement approaches and outcome definitions across studies. Further complicating research efforts is the challenge of isolating lithium's effects from other environmental factors, as lithium content in water often correlates with other minerals that may have independent health effects (Vita *et al.*, 2015). Researchers have also noted significant gaps in understanding regarding potential demographic variations in response to trace lithium exposure, with limited data on effects across different age groups, sexes, and genetic backgrounds.

6.2 Fortification and supplementation

The potential implementation of lithium fortification programs presents complex policy considerations regarding risk-benefit analysis at the population level (Memon *et al.,* 2020). While some researchers have proposed targeted supplementation for areas with naturally low lithium levels in drinking water, others caution about the potential unintended consequences of widespread supplementation without comprehensive safety data (Liaugaudaite *et al.,* 2017). Agricultural biofortification represents an emerging approach, where crops are selectively bred or modified to accumulate higher lithium concentrations (Sandhu *et al.,* 2023). Preliminary experiments with certain leafy vegetables and grains have demonstrated variable capacity for lithium uptake and accumulation, with factors such as soil pH and mineral composition significantly affecting bioavailability (Shahzad *et al.,* 2016). However, challenges remain in developing biofortified crops that maintain appropriate lithium levels without compromising plant growth, and nutritional profile, or introducing potential toxicity (Buendía-Valverde *et al.,* 2024). Research on consumer acceptance of lithium-biofortified foods remains limited, presenting another barrier to implementation alongside regulatory hurdles that currently classify such efforts differently from conventional nutrient fortification programs (Dhaliwal *et al.,* 2022). Establishing appropriate safety thresholds has proven challenging, with proposed provisional reference doses ranging considerably in the literature, reflecting lingering uncertainty about the precise boundary between beneficial exposure and potential toxicity (Schrauzer, 2002). Potentially vulnerable subpopulations require consideration in any fortification strategy, including pregnant women, individuals with renal impairment, and those taking medications that might interact with lithium (Post, 2018). Ethical considerations also permeate discussions of lithium supplementation, particularly given its historical association with psychiatric treatment and concerns about population-level neurobehavioral modifications.

6.3 Analytical challenges

Current methodologies for measuring trace lithium concentrations in biological samples and food sources face technical limitations that may contribute to inconsistent findings across studies (Shiotsuki *et al.,* 2016). Lithium levels in biological samples often fall near the detection limits of commonly available analytical equipment, necessitating specialized techniques like inductively coupled plasma mass spectrometry, which may not be accessible to all research facilities (Ishii *et al.,* 2015). The development of reliable biomarkers for assessing lithium status in humans remains an unresolved challenge, with debate continuing about whether serum, urine, or hair samples provide the most accurate reflection of long-term exposure (Dervic *et al.,* 2023). Standardization of lithium measurement protocols across laboratories would significantly advance the field by enabling more meaningful comparisons between studies (Kessing *et al.,* 2017). The absence of comprehensive lithium data in most food composition databases makes it difficult to accurately assess dietary intake and conduct nutritional epidemiological research (Schrauzer and de Vroey, 1994). Recent technological advances in analytical chemistry offer promising opportunities to address these limitations but remain widely implemented in lithium research (Rohiman *et al.,* 2023). Developing sensitive, cost-effective, and field-deployable methods for measuring trace lithium in various matrices would substantially advance both research capabilities and potential monitoring programs for fortification efforts (Chaudhary *et al.,* 2025).

7. Conclusion

The evidence surrounding lithium as a potential micronutrient presents a compelling case for reconsidering its role in human nutrition and health. Multiple lines of research from epidemiological studies linking environmental lithium exposure with improved mental health outcomes to molecular investigations revealing its diverse biological functions suggest that lithium may indeed play an essential role at trace levels well below therapeutic doses. While challenges remain in definitively establishing recommended intake levels and implementing appropriate public health strategies, the growing scientific consensus points toward lithium's importance in optimal physiological functioning, particularly for neurological health and emotional regulation. As research methodologies advance and our understanding deepen, the potential recognition of lithium as a micronutrient stands to significantly impact nutritional guidelines, agricultural practices, and public health initiatives, ultimately contributing to improved population health outcomes through optimized lithium nutrition.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article

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