MicroNutrients

Table 1 Roles of different micronutrients in Alzheimer's disease

Micronutrient	Key findings related to AD
Copper	Plaques of neurofibrillary tangle, amyloid, and soluble oligomers have large amounts of copper at their core[18]
	AD patients have significantly higher levels of copper in brain tissues[19-21]
	Copper promotes neurofibrillary tangle of hyperphosphorylation Tau and oxidative stress[22]
	Copper is useful marker for the diagnostic and prevention of AD[27]
Zinc	Zinc and selenium or iron and zinc have been concomitantly used to treat AD[35,36]
	Combination of zinc and copper accelerates the formation of amorphous aggregates of amyloid protein[40]
	High saturation magnetization of zinc ferrite improves the formation of amorphous aggregates of amyloid protein[41]
	Zinc increases the expression of amyloid precursor protein in a mouse model of AD[43]
	Zinc deficiency leads to a decrease in the learning ability and memory of AD mice[51]
Iron	Markedly increased concentration of ferritin and hemosiderin aggregates in the brain tissues of patients with severe AD[55]
	Iron dysregulation in brain neurons plays a key role in AD[57]
	Iron deposition increases Tau levels in brain tissue and promotes neurofibrillary Tangle Tau formation[10,59]
	Iron accelerates the deposition of amyloid proteins in brain tissues[60]
	Iron oxide nanoparticles have been used in clinical studies to improve AD[68]
Selenium	Chondroitin sulfate selenium improves spatial learning and memory impairment in mice with AD[75]
	The combination of nano-selenium and stem cells increases the levels of brain-derived neurotrophic factor and reduces amyloid deposition in AD mice[77]
	Selenium ameliorates the decrease of cognitive ability[78,79]
Silicon	Silicon may lower the risk of AD[82]
	The unique cross-linking ability of soluble silicic acid and its antagonism to toxic aluminum may protect against AD[83]
Manganese	Excessive intake of manganese can affect the structure and function of astrocytes, as well as the synthesis and degradation of glutamate. Effective control of manganese neurotoxicity may be a potential strategy for preventing or slowing AD[88]
	Abnormal conformation of prion proteins in normal cells can lead to their transformation into pathogenic prion proteins, which can bind to manganese, copper, and zinc, and thus induce AD[89]
	Manganese-rich nanocapsules improve cognitive ability in animal models with AD[93]
Arsenic	Sodium arsenite increases Tau phosphorylation and promotes the formation of neurofibrils in human neuroblastoma cells[94]
	Presence of arsenic in drinking water induces accumulation of amyloid proteins in the frontal cortex and hippocampus of AD mice[95]
	Sodium arsenite causes behavioral disorders and memory change in male AD rats[96]
	The levels of arsenic in the nails and hair of AD patients were higher than that in healthy controls[97]
Vitamin D	Vitamin D regulates innate and adaptive immune responses, which may play a role in the development of AD[98]
	Vitamin D enhances the immune function and may delay aging; thus, it may be used in AD treatment[99]

Aluminum(see silicon[silicic acid] for protective effect, also Chlorella,Parsley,Celantro)

from Food Additives: 0-95mg/day, average 24mg, Natural Sources: 1-10mg

https://pubmed.ncbi.nlm.nih.gov/30480226/ Aluminum Should Now Be Considered a Primary Etiological Factor in Alzheimer's Disease 2017

Aluminum acts as a catalyst for an earlier onset of Alzheimer's disease in individuals with or without concomitant predispositions, genetic or otherwise. Alzheimer's disease is not an inevitable consequence of aging in the absence of a brain burden of aluminum.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6682961/pdf/nutrients-11-01558.pdf The Nutritional Components of Beer and Its Relationship with Neurodegeneration and Alzheimer's Disease 2019

Aluminum is the most abundant metallic element in the Earth's crust and can be found in measurable quantities in food, soil, water, and air. The presence of **aluminum in water contributes highly to daily aluminum consumption**. Although this metal is normally found in trace amounts in the drinking water, the possibility for low-dose chronic exposure should not be discarded [22]. In addition, the widespread use of products made from, or containing, aluminum ensures the presence of this metal in our bodies. Several years have passed since the first time that **experts strongly claimed that human exposure to aluminum should be limited as it can exert deleterious effects even at small concentrations** [23 , 24]. Nonetheless, it should be pointed out that the deleterious effects of aluminum in healthy individuals, though inevitable, will be low at normal exposure levels because of their **low gastrointestinal uptake and bioavailability, and relatively high urinary excretion [25].** The **hypothesis linking aluminum consumption and Alzheimer's disease, although highly controversial, has been supported by several epidemiological studies** [26, 27]. In addition, several studies in animal models have given light to this relationship. Therefore, experimental studies in rats and mice showed that aluminum accumulates in the brain cortex, hippocampus, and cerebellum [28], promoting the phosphorylation and aggregation of highly phosphorylated proteins, such as tau protein [29]. Other authors [17] have reported that the amygdala and the hippocampus are the brain areas with the highest aluminum content in an Alzheimer's disease model. In addition, Oshiro et al. [30] reported that aluminum accumulates more in glial cells than in neurons. The **brain has been found to be the target organ for aluminum accumulation**; hence, this element can be primarily considered as a neurotoxic [31] Walton [36] and Bolognin et al. [37] suggested that aluminum is engaged in the brain's neurofibrillary tangles formation by promoting the expression of the Amyloid precursor protein (APP) of the AP and increasing the levels of β-

40 and β-42 fragments in the brain and should, therefore, be considered as a causative factor in Alzheimer's disease. In addition, aluminum appears to be associated with AP in the brain [38 , 39], as the chronic application of this metal caused the accumulation of AP in cultured neurons of rat cerebral cortex and in neuroblastoma cells. It is known that the monomeric form of AP has a random coiled structure, while the oligomeric AP have pleated sheet structures and form insoluble aggregates, named amyloid fibrils. The neurotoxicity of AP peptides has been studied in an aging model compared to freshly prepared AP in cultured neurons, and it has been demonstrated that the soluble oligomers are synaptotoxic and neurotoxic [35]. On the other hand, this metal can cause pro-oxidant activity. Exley [38] reported that this effect might be explained by the formation of an aluminum superoxide semireduced ion radical (AlO22+). **In Alzheimer's disease transgenic mice models, dietary aluminum markedly increased lipid peroxidation and Aß-level presence** [40]. In isolated systems, **aluminum may increase the oxidative stress produced by transition metals such as iron [41] or copper [42].** In line with this observation, o**ur group recently reported that aluminum intoxication contributes to a metal imbalance in the brain**, which in turn would be responsible for this organ oxidation and reduced antioxidant capacity [43]. Our results are in line with those of several authors who described that Al3+ decreased the activity of the antioxidant enzymes catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) [44 ,45]. Sharma et al. [46] found an **increase of oxidative stress** in the brain and serum with **low reduced glutathione (GSH)**, GPx, CAT, and SOD levels after 10 weeks of aluminum chloride gavages exposure. Moumen et al. [47] reported increased concentrations of tiobarbituric acid reactive substances (TBARS) and glutathione S-transferase after aluminum intoxication.

https://pubmed.ncbi.nlm.nih.gov/21157018/ Aluminum and Alzheimer's disease: after a century of controversy, is there a plausible link? 2011

Misconceptions about Al bioavailability may have misled scientists regarding the significance of Al in the pathogenesis of AD. The hypothesis that Al significantly contributes to AD is built upon very solid experimental evidence and should not be dismissed. Immediate steps should be taken to lessen human exposure to Al, which may be the single most aggravating and avoidable factor related to AD.

https://pubmed.ncbi.nlm.nih.gov/11130287/ The toxicology of aluminum in the brain: a review 2000

Al is a neurotoxicant in animals and humans. It has been implicated in the etiology of sporadic Alzheimer's disease (AD) and other neurodegenerative disorders, although this is highly controversial. This controversy has not been resolved by epidemiological studies, as only some found a small association between increased incidence of dementia and drinking water Al concentration. Studies of brain Al in AD have not produced consistent findings and have not resolved the controversy. Injections of Al to animals produce behavioral, neuropathological and neurochemical changes that partially model AD. Aluminum has the ability to produce neurotoxicity by many mechanisms. Excess, insoluble amyloid beta protein (A beta) contributes to AD. **Aluminum promotes formation and accumulation of insoluble A beta and hyperphosphorylated tau.** To some extent, **Al mimics the deficit of cortical cholinergic neurotransmission seen in AD. Al increases Fe-induced oxidative injury.**

https://pubmed.ncbi.nlm.nih.gov/28889268/ Aluminum and Alzheimer's Disease 2017

Despite some factors influence individual bioavailability to this metal after oral, dermal, or inhalation exposures, h**umans are considered to be protected against Al toxicity because of its low absorption and efficient renal excretion**. However, s**everal factors can modify Al absorption and distribution through the body,** which may in turn progressively contribute to the development of silent chronic exposures that may lately trigger undesirable consequences to health. For instance, Al has been recurrently shown to cause encephalopathy, anemia, and bone disease in dialyzed patients. On the other hand, it remains controversial whether **low doses of this metal may contribute to developing Alzheimer's disease (AD)**, probably because of the multifactorial and highly variable presentation of the disease.This chapter primarily focuses on two key aspects related to Al neurotoxicity and AD, which are metabolic impairment and **iron (Fe) alterations.**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3056430/ Link between Aluminum and the Pathogenesis of Alzheimer's Disease: The Integration of the Aluminum and Amyloid Cascade Hypotheses 2011

Whilst being environmentally abundant, aluminum is not essential for life. On the contrary, **aluminum is a widely recognized neurotoxin that inhibits more than 200 biologically important functions and causes various adverse effects in plants, animals, and humans.** The relationship between aluminum exposure and neurodegenerative diseases, including dialysis encephalopathy, amyotrophic lateral sclerosis and Parkinsonism dementia in the Kii Peninsula and Guam, and Alzheimer's disease (AD) has been suggested. **In particular, the link between aluminum and Alzheimer's disease has been the subject of scientific debate for several decades. However, the complex characteristics of aluminum bioavailability make it difficult to evaluate its toxicity and therefore, the relationship remains to be established**. Mounting evidence has suggested that significance of oligomerization of *β*-amyloid protein and neurotoxicity in the molecular mechanism of AD pathogenesis. **Aluminum may play crucial roles as a cross-linker in *β*-amyloid oligomerization**. Here, we review the detailed characteristics of aluminum neurotoxicity based on our own studies and the recent literatures. Our aim is to revisit the link between aluminum and AD and to integrate aluminum and amyloid cascade hypotheses in the context of *β*-amyloid oligomerization and the interactions with other metals.

The evidence now suggests that the significance of Al in the pathogenesis of AD should be concerned. Other metals usually share the binding site of one metal ion, although their binding constants differ. Al binds to various metal-binding proteins and influences metal homeostasis. The i**nteractions between Al and other metals should be considered** owing to the implications of various trace elements in the pathogenesis of AD.

In this review, we have summarized the properties associated with various aspects of Al neurotoxicity. There is **growing evidence for a link between Al and AD, and between other metals and AD**. Nevertheless, because the precise mechanism of AD pathogenesis remains unknown, this **issue is controversial.** However, it is **widely accepted that Al is a recognized neurotoxin, and that it could cause cognitive deficiency and dementia when it enters the brain** and may have various adverse effects on CNS.

https://pubmed.ncbi.nlm.nih.gov/28159219/ **Aluminium in brain tissue in familial Alzheimer's disease 2017**

We have made the **first ever measurements of aluminium in brain tissue from 12 donors diagnosed with familial Alzheimer's disease**. The **concentrations of aluminium were extremely high, for example, there were values in excess of 10μg/g tissue dry wt. in 5 of the 12 individuals.** Overall, the concentrations were higher than all previous measurements of brain aluminium except cases of known aluminium-induced encephalopathy. We have supported our quantitative analyses using a novel method of aluminium-selective fluorescence microscopy to visualise aluminium in all lobes of every brain investigated. The unique quantitative data and the stunning images of **aluminium in familial Alzheimer's disease brain tissue raise the spectre of aluminium's role in this devastating disease**.

https://pubmed.ncbi.nlm.nih.gov/16949191/ Aluminum bioavailability from the approved **food additive** leavening agent acidic **sodium aluminum phosphate**, incorporated into a baked good, is lower than from water 2006

Foods contribute approximately 95% and drinking water 1-2% of the typical human's daily Al intake. The objectives were to estimate oral Al bioavailability from a representative food containing the food additive acidic sodium aluminum phosphate (acidic SALP), a leavening agent in baked goods. **Oral Al bioavailability (F) from biscuit containing 1% or 2% acidic (26)Al-SALP averaged approximately 0.11% and 0.13%; significantly less than from water, which was previously shown to be approximately 0.3%.** The time to maximum serum (26)Al concentration was 4.2 and 6h after consumption of biscuit containing 1% or 2% (26)Al-acidic SALP, respectively, compared to 1-2h following (26)Al in water. These results of oral Al bioavailability from acidic (26)Al-SALP in a biscuit (F approximately 0.1%) and results from (26)Al in water (F approximately 0.3%) x the contributions of food and drinking water to the typical human's daily Al intake (approximately 5-10mg from food and 0.1mg from water, respectively) **suggest food provides approximately 25-fold more Al to systemic circulation, and potential Al body burden, than does drinking water.**

https://pubmed.ncbi.nlm.nih.gov/18436363/ Aluminum bioavailability from basic sodium aluminum phosphate, an approved food additive emulsifying agent, incorporated in cheese 2008

It was suggested that oral Al bioavailability from drinking water is much greater than from foods. The objective was to further test this hypothesis. Oral Al bioavailability was determined in the rat from basic [26Al]-sodium aluminum phosphate (basic SALP) in a process cheese. Consumption of approximately 1g cheese containing 1.5% or 3% basic SALP resulted in oral Al bioavailability (F) of approximately **0.1% and 0.3%, r**espectively, and time to maximum serum 26Al concentration (Tmax) of 8-9h. These Al bioavailability results were intermediate to previously reported results from **drinking water (F approximately 0.3%)** and acidic-SALP incorporated into a biscuit (F approximately 0.1%), using the same methods. Considering the **similar oral bioavailability of Al from food vs. water, and their contribution to the typical human's daily Al intake (approximately 95% and 1.5%, respectively), these results suggest food contributes much more Al to systemic circulation, and potential Al body burden, than does drinking water.** These results do not support the hypothesis that drinking water provides a disproportionate contribution to total Al absorbed from the gastrointestinal tract.

https://pubmed.ncbi.nlm.nih.gov/18848597/ Aluminum bioavailability from tea infusion 2008

Bioavailability from tea averaged 0.37%; not significantly different from water (F=0.3%), or basic sodium aluminum phosphate (SALP) in cheese (F=0.1-0.3%), but greater than acidic SALP in a biscuit (F=0.1%). These results of oral Al bioavailability x daily consumption by the human suggest **tea can provide a significant amount of the Al that reaches systemic circulation.** This can allow distribution to its target organs of toxicity, the central nervous, skeletal and hematopoietic systems. **Further testing of the hypothesis that Al contributes to Alzheimer's disease may be more warranted with studies focusing on total average daily food intake, including tea and other foods containing appreciable Al**, than drinking water.

https://pubmed.ncbi.nlm.nih.gov/17004365/ Aluminum and Alzheimer's disease, a personal perspective after 25 years 2006

It is now 25 years since the publication of our original paper investigating the association aluminum with Alzheimer's disease. This publication reported on the results of scanning electron microscopy coupled x-ray spectrometry microprobe elemental studies of both neurofibrillary tangle-bearing and tangle-free neurons in the hippocampus of cases of Alzheimer's disease and controls. Peaks related to the presence o**f aluminum were consistently detected within the tangle-bearing neurons**. This paper supported the association of aluminum and Alzheimer's disease on the cellular level of resolution and caused considerable interest and discussion. Subsequent work demonstrated prominent **evidence of aluminum accumulation in the tangle-bearing neurons of cases of amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam**. This latter observation has now been replicated using five different forms of microanalysis. Finally, using laser microprobe mass analysis, we demonstrated that the **abnormally high aluminum-related signal which we originally detected was actually located within the neurofibrillary tangle, itself, and was accompanied by excess concentrations of iron.** Although it is **unlikely that aluminum represents an etiologic cause of Alzheimer's disease, we believe that this highly reactive element, known to cross-link hyperphosphorylated proteins, may play an active role in the pathogenesis of critical neuropathologic lesion in Alzheimer's disease and other related disorders**.

https://pubmed.ncbi.nlm.nih.gov/1490425/ Dietary and other sources of aluminium intake 1992

Thus most adults consume 1-10 mg aluminium daily from natural sources. Cooking in aluminium containers often results in statistically significant, but not practically important, increases in the aluminium content of foods. Intake of aluminium from **food additives varies greatly (0 to 95 mg Al daily) among residents in North America, with the median intake for adults being about 24 mg daily**. Generally, the intake of aluminium from foods is less than 1% of that consumed by individuals using aluminium-containing pharmaceuticals. Currently the real scientific question is not the amount of aluminium in foods but the availability of the aluminium in foods and the sensitivity of some population groups to aluminium. Several dietary factors, including **citrate**, may affect the absorption of aluminium.

Arsenic

Average intake: 2ug/day

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9372870/pdf/WJCC-10-7631.pdf Role of micronutrients in Alzheimer's disease: Review of available evidence 2022

Arsenic is an essential micronutrient of the body. It is widely found in nature in the form of Ash, black, and yellow arsenic. Arsenic is highly toxic, but **in small amounts it is beneficial.** Arsenic participates in biotransformation, protein synthesis, and material metabolism. Sodium arsenite (1–10 mol/L) was shown to increase Tau phosphorylation and **promote the formation of neurofibrils in human neuroblastoma SH-SY5Y cells, which are used to study AD**. This effect was related to the activation of Erk Pathway by sodium arsenite[89]. Animal studies have shown that arsenic in drinking water can cause abnormal circadian rhythm and movement behavior in mice with AD, as well as accumulation of amyloid proteins in the frontal cortex and hippocampus. This was found to be related to arsenic-induced lipid peroxidation in mice[90]. Sodium arsenite was shown to cause behavioral disorders and memory change in male rats with AD, which was alleviated by gallic acid (100 mg/kg); this indicated the neuroprotective effect of gallic acid [91]. In a clinical study, arsenic levels were measured in the nails and hair of 40 individuals with AD using inductively coupled plasma mass spectrometry. **Arsenic levels in AD were higher than those in controls.** This implies that **individuals with AD often have elevated levels of arsenic[92].**

https://www.ncbi.nlm.nih.gov/books/NBK222322/

Because **organic forms of arsenic are less toxic than inorganic forms**, any increased health risk from intake of organic arsenic from food products such as fish is unlikely.

https://pubmed.ncbi.nlm.nih.gov/20473132/ The arsenic exposure hypothesis for Alzheimer disease 2010

Prior research has shown that **arsenic exposure induces changes that coincide with most of the developmental, biochemical, pathologic, and clinical features of Alzheimer disease (AD)** and associated disorders. On the basis of this literature, we propose the Arsenic Exposure Hypothesis for AD that is inclusive of and cooperative with the existing hypotheses. Arsenic exposure invokes brain inflammatory responses, which resonates with the inflammatory hypotheses of AD. **Arsenic exposure has been linked to reduced memory and intellectual abilities in children** and adolescents, which provides a biologic basis for the developmental origin of health and disease hypothesis for AD. Arsenic and its metabolites generate free radicals causing oxidative stress and neuronal death, which fits the existing oxidative stress hypothesis. Taken together, the **arsenic exposure hypothesis for AD provides a parsimonious testable hypothesis for the development and progression of this devastating disease at least for some subsets of individuals.**

https://pubmed.ncbi.nlm.nih.gov/30141907/ Arsenic Exposure Contributes to the Bioenergetic Damage in an Alzheimer's Disease Model 2018

In order to determine whether iAs promotes the pathophysiological progress of AD, we used the 3xTgAD mouse model. Mice were exposed to iAs in drinking water from gestation until 6 months (As-3xTgAD group) and compared with control animals without arsenic (3xTgAD group). The bioenergetic profile revealed **decreased ATP levels** accompanied by the decline of complex I, and an oxidant state in the hippocampus. In conclusion, **mitochondrial dysfunction may be one of the triggering factors through which chronic iAs exposure exacerbates brain AD-like pathology.**

https://pubmed.ncbi.nlm.nih.gov/31962196/ Positive association between **soil arsenic concentration and mortality from alzheimer's disease** in mainland China 2020

Results: The spearman correlation coefficient between As concentration and AD mortality was 0.552 (p = 0.004), 0.616 (p = 0.001) and 0.622 (p = 0.001) in the A soil As (eluvial horizon), the C soil As (parent material horizon), and the Total soil As (A soil As + C soil As), respectively. When the A soil As concentration was over 9.05 mg/kg, 10.40 mg/kg and 13.10 mg/kg, the relative risk was 0.835 (95 % CI: 0.832, 0.838), 1.969 (95 %CI: 1.955, 1.982), and 2.939 (95 % CI: 2.920, 2.958), respectively; **when the C soil As reached 9.45 mg/kg, 11.10 mg/kg and 13.55 mg/kg, the relative risk was 4.349 (95 % CI: 4.303, 4.396), 6.108 (95 % CI: 6.044, 6.172), and 9.125 (95 %CI: 9.033, 9.219), respectively**. No correlation was found between lead, cadmium, and mercury concentration in the soil and AD mortality.

Conclusion: There was an apparent soil As concentration dependent increase in AD mortality. Results of this study may provide evidence for a **possible causal linkage between arsenic exposure and the death risk from AD.**

https://pubmed.ncbi.nlm.nih.gov/35742553/ Alzheimer's Disease Association with Metals and Metalloids Concentration in Blood and Urine. 2022

As there is some evidence that the risk for Alzheimer's disease (AD) is partially attributable to environmental exposure to some metals and metalloids, we examined an association between AD and arsenic, chromium, and selenium in 53 AD patients and 217 controls. **In AD patients, urinary arsenic and blood chromium were significantly higher, while blood selenium was significantly lower compared to controls.**

https://pubmed.ncbi.nlm.nih.gov/30025849/ Risk of Alzheimer's disease with metal concentrations in whole blood and urine: A case-control study using propensity score matching 2018

In addition, people with a low median level of selenium and high median level of InAs%, or/and a low median level of DMA% had approximately two- to threefold significant AD risk. **Urinary arsenic profiles may be associated with increased AD risk.**

Boron (anti-oxidant, metal chelator, inhibit AchE, works with other supplements)

acceptable Range: 1-13mg/day

https://pubmed.ncbi.nlm.nih.gov/30568754/ Discovery of boron-containing compounds as Aβ aggregation inhibitors and antioxidants for the treatment of Alzheimer's disease. 2018

A novel series of boron-containing compounds were designed, synthesized and evaluated as multi-target-directed ligands against Alzheimer's disease. The biological activity results demonstrated that these compounds possessed a **significant ability to inhibit self-induced Aβ aggregation** (20.5-82.8%, 20 μM) and to act as **potential antioxidants** (oxygen radical absorbance capacity assay using fluorescein (ORAC-FL) values of 2.70-5.87). In particular, compound 17h is a potential lead compound for AD therapy (IC50 = 3.41 μM for self-induced Aβ aggregation; ORAC-FL value = 4.55). Compound 17h also **functions as a metal chelator**. These results indicated that **boron-containing compounds could be new structural scaffolds for the treatment of AD.**

https://pubmed.ncbi.nlm.nih.gov/34825189/ **Boron-based hybrids** as novel scaffolds for the development of drugs with neuroprotective properties 2021

Novel **boron-based compounds (BBCs)** were synthesized and evaluated as potential candidates for the development of novel drugs against Alzheimer's disease (AD). The neuroprotective profile of novel BBCs was evaluated using Aβ1-42-treated-SH-SY5Y cells while their antioxidant activity was evaluated by total antioxidant capacity (TAC) and total oxidative status (TOS) assays. Results showed that BLA (a novel boron-based hybrid containing an antioxidant portion) inhibited cell death induced by Aβ1-42-exposure in differentiated SH-SY5Y cells, resulting in an increase in cell viability by 25-33% (MTT assay) and by 63-71% (LDH assay) in a concentration range of 25-100 μM. Antioxidant assays demonstrated a good capability of BLA to counteract the oxidative status. Moreover, BLA possessed a significant ability to **inhibit acetylcholinesterase (AChE)** (22.96% at 50 μM), an enzyme whose enzymatic activity is increased in AD patients. In the present work, absorption and distribution properties of boron-based hybrids were predicted using Pre-ADMET software. In vitro preliminary results suggested that boron-based hybrids could be new structural scaffolds for the development of novel drugs for the management of AD.

https://pubmed.ncbi.nlm.nih.gov/35897815/ Boron Nitride Nanoparticles Loaded with a Boron-Based Hybrid as a Promising Drug Carrier System for Alzheimer's Disease Treatment. 2022

further investigations and enlightened neuroprotective capabilities of **boron molecules to treat AD and other neurodegenerative diseases**.

https://pubmed.ncbi.nlm.nih.gov/33237490/ Effects of **Curcumin and Boric Acid** Against Neurodegenerative Damage Induced by Amyloid Beta (1-42). 2021

Curcumin and BA + curcumin combination showed an enhancement in synaptophysin levels of Aβ1-42-induced synaptosomes (P < 0.01). The **results showed that BA and curcumin had protective effects on rat brain synaptosomes against Aβ1-42 exposure.** BA and curcumin treatment can have abilities to prevent the alterations of the cholinergic system and inhibit oxidative stress in the cerebral cortex synapses of Aβ1-42 exposed.

https://pubmed.ncbi.nlm.nih.gov/32041435/ Investigation of the protective effects of boric acid on ethanol induced kidney injury. 2020

BA acted as an antioxidant against renal tubule injury caused by chronic use of ethanol. **BA protects against apoptosis in renal tubules by decreasing oxidative damage**.

https://pubmed.ncbi.nlm.nih.gov/36006107/ **Boron Compounds Exhibit Protective Effects against Aluminum-Induced Neurotoxicity** and Genotoxicity: In Vitro and In Vivo Study. 2022

However, the boron compounds alone did not cause adverse changes based on the above-studied parameters. Moreover, these compounds exhibit different levels of beneficial effects by **removing the harmful impact of Al.** The antioxidant, antigenotoxic and cytoprotective effects of boron compounds against Al-induced damage indicate that boron may have a high potential for use in medical purposes in humans. In conclusion, our analysis suggests that **boron compounds (especially BA(boric acid), BX(borax) and UX(ulexite) can be administered to subjects to prevent neurodegenerative** and hematological disorders at determined doses.

https://pubmed.ncbi.nlm.nih.gov/20663653/ The effects of some boron compounds against heavy metal toxicity in human blood. 2012

Whereas, the tested boron compounds (5-20 ppm) **significantly reduced the genotoxic effects induced by low doses of heavy metals.** Our results revealed that the protective roles of boron compounds occurred with the effectiveness on their anti-oxidant capacity. In conclusion, these compounds could be **useful in the development of functional food and raw materials of medicine.**

https://pubmed.ncbi.nlm.nih.gov/7889884/ Dietary boron, brain function, and cognitive performance. 1994

Although the trace element boron has yet to be recognized as an essential nutrient for humans, recent data from animal and human studies suggest that boron may be important for mineral metabolism and membrane function. To investigate further the functional role of boron, brain electrophysiology and cognitive performance were assessed in response to dietary manipulation of boron (approximately 0.25 versus approximately 3.25 mg boron/2000 kcal/day) in three studies with healthy older men and women. Within-subject designs were used to assess functional responses in all studies. Spectral analysis of electroencephalographic data showed effects of dietary boron in two of the three studies. When the low boron intake was compared to the high intake, there was a significant ($p < 0.05$) increase in the proportion of low-frequency activity, and a decrease in the proportion of higher-frequency activity, an effect often observed in response to general malnutrition and heavy metal toxicity. Performance (e.g., response time) on various cognitive and psychomotor tasks also showed an effect of dietary boron. When contrasted with the high boron intake, **low dietary boron resulted in significantly poorer performance ($p < 0.05$) on tasks emphasizing manual dexterity (studies II and III); eye-hand coordination (study II); attention (all studies); perception (study III); encoding and short-term memory (all studies); and long-term memory (study I).** Collectively, the data from these three studies indicate that boron may play a role in human brain function and cognitive performance, and provide additional evidence that boron is an essential nutrient for humans.

https://pubmed.ncbi.nlm.nih.gov/35618890/ Investigation Covering the Effect of Boron plus Taurine Application on Protein Carbonyl and Advanced Oxidation Protein Products Levels in Experimental Alzheimer Model 2022

Boron, regarded as a **potential antioxidant,** has the effect of reducing oxidative stress. Taurine, as one of the thiol-containing amino acids, exists at different concentrations in both the neurons and

glial cells of the central nervous system. It plays an important role in the protective and adjuvant therapies as an antioxidant due to its characteristics of maintaining the oxidant-antioxidant balance of the body as well as cell integrity and increasing body resistance. Our findings suggested that **taurine alone and co-administration of boron and taurine had a decreasing effect on AOPP and PC levels of the experimental Alzheimer model of the rats**.

https://pubmed.ncbi.nlm.nih.gov/35544753/ Prevent Drug Leakage via the Boronic Acid Glucose-Insensitive Micelle for Alzheimer's Disease Combination Treatment. 2022

Boronic acid (BA) materials have been **widely applied to glucose and oxidative stress-sensitive drug delivery** for the treatment of cancer, diabetes, and Alzheimer's disease (AD). There are completely various BA-sensitive delivery conditions in different diseases. BA materials in the treatment of diabetes show better performance at a high-glucose environment than normal. In contrast, the concentration of glucose in the brain is much lower than that in the blood of AD patients. This work provided excellent antioxidant drugs (vitamin E succinate, melatonin, and quercetin) and a glucose metabolism drug (insulin) loaded in GIM micelle for AD treatment. The discovery of the **combination mechanism is enormously valuable for AD clinical research**.

https://pubmed.ncbi.nlm.nih.gov/34253017/ A Boron-Containing Compound Acting on Multiple Targets Against Alzheimer's Disease. Insights from Ab Initio and Molecular Dynamics Simulations. 2021

Given the multifactorial nature and pathogenesis of Alzheimer's disease, therapeutic strategies are addressed to combine the benefits of every single-target drug into a sole molecule. Quantum mechanics and molecular dynamics (MD) methods were employed here to investigate the **multitarget action of a boron-containing compound against Alzheimer's disease.** The antioxidant activity as a radical scavenger and **metal chelator** was explored by means of density functional theory. The most plausible radical scavenger mechanisms, which are hydrogen transfer, radical adduct formation, and single-electron transfer in aqueous and lipid environments, were fully examined. Metal chelation ability was investigated by considering the complexation of Cu(II) ion, one of the metals that in excess can even catalyze the β-amyloid (Aβ) aggregation. The most probable complexes in the physiological environment were identified by considering both the stabilization energy and the shift of the λmax induced by the complexation. The excellent capability to **counteract Aβ aggregation** was explored by performing MD simulations on protein-ligand adducts, and the activity was compared with that of curcumin, chosen as a reference.

Cadmium **(Gallic and ascorbic acids supplementation helps, also Black Seed Oil, Zinc)**

Sources: Cigarette smoke, seafood, organ meats(kidney), (Grains, and vegs end up being highest contributors, but bio-availability low)

https://pubmed.ncbi.nlm.nih.gov/32651318/ Heavy Metals Exposure and Alzheimer's Disease and Related Dementias. 2020

Adult human epidemiologic studies have consistently shown lead, cadmium, and manganese are associated with impaired cognitive function and cognitive decline. Given the widespread and global exposure to lead, cadmium, and manganese, even small increases in the risks of Alzheimer's disease and related dementias would have a major population impact on the burden on disease.

https://pubmed.ncbi.nlm.nih.gov/28511080/ Cadmium and Alzheimer's disease mortality in U.S. adults: Updated evidence with a urinary biomarker and extended follow-up time 2017

Cadmium has been linked to impaired cognitive function in adults and may cause behavioral, physiological and molecular abnormalities characteristic of Alzheimer's disease (AD) in animals. **Evidence linking cadmium and AD in humans is limited, but supportive.** In the most recent epidemiologic study, blood cadmium in U.S. adults was positively associated with elevated AD mortality 7-13 years later. An interquartile range (IQR; IQR=0.51ng/mL) increase in **urinary cadmium was associated with 58% higher rate of AD mortality** (hazard ratio (HR)=1.58, 95% CI: 1.20, 2.09. p-value=0.0009, mean follow-up: 7.5 years) in NHANES 1999-2006 participants. **In contrast,** in NHANES III participants, an IQR (IQR=0.78ng/mL) **increase in urinary cadmium was not associated with AD mortality (HR=0.85,** 95% CI: 0.63, 1.17, p-value=0.31, mean follow-up: 13 years). Also in the NHANES III sample however, when the maximum follow-up time was restricted to 12.7 years (i.e. the same as NHANES 1999-2006 participants) and urinary creatinine adjustments were not made, urinary cadmium was associated with elevated AD mortality (HR=1.11, 95% CI: 1.02, 1.20, p-value=0.0086). **Our study partially supported an association between cadmium and AD mortality,** but the sensitivity of results to follow-up time and creatinine adjustments necessitate cautious interpretation of the association.

https://pubmed.ncbi.nlm.nih.gov/27301955/ Blood cadmium levels and Alzheimer's disease mortality risk in older US adults 2016

Of the 4,064 participants, 51 subjects died as a result of AD. **Compared with participants with low blood cadmium levels (≤0.3 μg/L), those with high cadmium levels (>0.6 μg/L) exhibited a 3.83-fold (hazard ratio = 3.83; 95 % CI = 1.39-10.59) increased risk of AD mortality.** In the Kaplan-Meier survival curves for cumulative AD mortality, higher levels of blood cadmium showed marginally significant association with increased mortality at baseline and in patients over 60 years of age (p = 0.0684).

https://pubmed.ncbi.nlm.nih.gov/34248598/ Cadmium, an Environmental Contaminant, Exacerbates Alzheimer's Pathology in the Aged Mice's Brain 2021

Cadmium (Cd) is an environmental contaminant, which is a potential risk factor in the progression of aging-associated neurodegenerative diseases. Herein, we have assessed the effects of chronic administration of Cd on cellular oxidative stress and its associated Alzheimer's disease (AD) pathologies in animal models. Two groups of mice were used, one group administered with saline and the other with Cd (1 mg/kg/day; intraperitoneally) for 3 months. After behavioral studies, molecular/biochemical (Immunoblotting, ELISAs, ROS, LPO, and GSH assays) and morphological analyses were performed. We observed an **exacerbation of memory and synaptic deficits in chronic Cd-injected mice.** These findings suggest the regulation of oxidative stress/ROS and its associated amyloid beta pathologies for targeting the Cd-exacerbated AD pathogenesis.

https://pubmed.ncbi.nlm.nih.gov/36002551/ Gallic and ascorbic acids supplementation alleviate cognitive deficits and neuropathological damage **exerted by cadmium chloride** in Wistar rats 2022

Cadmium is a highly neurotoxic heavy metal that interferes with DNA repair mechanisms via generation of reactive oxygen species. The potentials of polyphenols and antioxidants as effective protective agents following heavy metal-induced neurotoxicity are emerging. We therefore explored the neuroprotective potentials of gallic and ascorbic acids in $CdCl_2$-induced neurotoxicity. The Morris Water Maze test revealed significant increase in escape latency in $CdCl_2$ group relative to rats concurrently treated with GA or AA. Similarly, time spent in the target quadrant was reduced significantly in $CdCl_2$ group relative to other groups. Concomitant administration of gallic acid led to significant reduction in the durations of immobility and freezing that were elevated in $CdCl_2$ group during forced swim and open field tests respectively. Furthermore, GA and AA restored myelin integrity and neuronal loss observed in the $CdCl_2$ group. We conclude that **gallic and ascorbic acids enhance learning and memory, decrease anxiety and depressive-like behavior in $CdCl_2$-induced neurotoxicity with accompanying myelin-protective ability.**

https://pubmed.ncbi.nlm.nih.gov/32452325/ Evaluation of Blood Oxidant/Antioxidant Changes and Testicular Toxicity after Subacute Exposure to Cadmium in Albino Rats: Therapeutic Effect of *Nigella sativa* Seed Extracts 2021

This study aimed to evaluate the ameliorative effect of methanolic extracts of Nigella sativa (MENS) against **cadmium-induced blood oxidative stress** and testicular toxicity in albino rats. Histopathological studies on the testes showed that cadmium significantly induced testicular injury, which was however ameliorated by the seed extract of N. sativa.

Conclusion: We conclude that **N. sativa seed extract is potentially testiculoprotective and attenuates oxidative stress against harmful chemical toxins such as cadmium.**

https://pubmed.ncbi.nlm.nih.gov/34912029/ Cadmium exposure modulates the gut-liver axis in an Alzheimer's disease mouse model 2021

The human Apolipoprotein E4 (ApoE4) variant is the strongest known genetic risk factor for Alzheimer's disease (AD). Cadmium (Cd) has been shown to impair learning and memory at a greater extent in humanized ApoE4 knock-in (ApoE4-KI) mice as compared to ApoE3 (common allele)-KI mice. Here, we determined how cadmium interacts with ApoE4 gene variants to modify the gut-liver axis. In conclusion, **Cd exposure profoundly modified the gut-liver axis in the most susceptible mouse strain to neurological damage** namely the ApoE4-KI males, evidenced by an increase in microbial AD biomarkers, reduction in energy supply-related pathways in gut and blood, and an increase in hepatic pathways involved in inflammation and xenobiotic biotransformation.

https://alzheimers.news/2021-08-04-cadmium-alzheimers-risk-gene-cognitive-impairment.html

Zhengui Xia, a professor of toxicology at *Washington University* and one of the study's researchers, commented: "Exposure to cadmium through our daily lives could have a detrimental effect on our cognition. If you have the APOE4 gene, the risk is significantly higher."

https://pubmed.ncbi.nlm.nih.gov/33375344/ Zinc and Cadmium in the Aetiology and Pathogenesis of Osteoarthritis and Rheumatoid Arthritis 2020

Cadmium interferes with zinc's functions and there is increased uptake under zinc deficiency.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8027184/ Zinc as a countermeasure for cadmium toxicity 2021

Cadmium (Cd) is an important environmental pollutant and long-term Cd exposure is closely related to autoimmune diseases, cancer, cardiovascular diseases (CVD), and hepatic dysfunction. Zinc (Zn) is an essential metal that plays key roles in protein structure, catalysis, and regulation of their function. **Numerous studies have shown that Zn can reduce Cd toxicity;**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4743362/ Effect of parsley (*Petroselinum crispum*, Apiaceae) juice against cadmium neurotoxicity in albino mice (*Mus Musculus*) 2016

The low dose (5 g/kg/day) of **parsley exhibited beneficial effects in reducing the deleterious changes associated with Cd treatment** on the behavior, neurotransmitters level, oxidative stress and brain neurons of the Cd-treated mice.

https://nutritionfacts.org/2015/10/15/how-to-reduce-your-dietary-cadmium-absorption/ How to Reduce Your Dietary Cadmium Absorption 2015

In fact, there is a significant *decrease* in the hair concentrations of lead and cadmium after the change from an omnivorous to a vegetarian diet, indicating a lower absorption of the metals. Researchers took folks eating a standard Swedish diet and put them on a vegetarian diet. The vegetarians were encouraged to eat lots of whole, unrefined plant foods, with no meat, poultry, fish, and eggs. Junk food was also discouraged. Within **three months on a vegetarian diet, their levels significantly dropped, and stayed down for the rest of the year-long experiment.** The researchers came back three years later, three years after the subjects stopped eating vegetarian, and found that their levels of mercury, cadmium, and lead had shot back up.

Chromium

Sources: meat,grain,fruits,vegs,nuts,spices. (content varies 50 fold in growing and processing)

RDA: 30mcg Male, 20mcg Female

https://pubmed.ncbi.nlm.nih.gov/9380836/ Chromium as an essential nutrient for humans 1997

Chromium is an essential nutrient required for sugar and fat metabolism. Normal dietary intake of Cr for humans is suboptimal. The estimated safe and adequate daily dietary intake for Cr is 50 to 200 microg. However, **most diets contain less than 60% of the minimum suggested intake of 50 microg**. Insufficient dietary intake of Cr leads to signs and symptoms that are similar to those observed for diabetes and cardiovascular diseases. Supplemental Cr given to people with impaired glucose tolerance or diabetes leads to improved blood glucose, insulin, and lipid variables. Chromium has also been shown to improve lean body mass in humans and swine. Response to Cr is dependent upon form and amount of supplemental Cr. Chromium is a nutrient; therefore, it will only be of benefit to those who are marginally or overtly Cr deficient. **Trivalent Cr has a very large safety range** and there have been no documented signs of Cr toxicity in any of the nutritional studies at levels up to 1 mg per day.

https://pubmed.ncbi.nlm.nih.gov/31898080/ Chromium picolinate attenuates cognitive deficit in ICV-STZ rat paradigm of sporadic Alzheimer's-like dementia via targeting neuroinflammatory and IRS-1/PI3K/AKT/GSK-3β pathway 2020

In our study, streptozotocin (STZ) in a dose of 3 mg/kg was injected in male Wistar rats bilaterally through the intracerebroventricular (ICV) route on stereotaxic apparatus. **Chromium picolinate (CrPic)** was tested at doses of 1 mg/kg, 2 mg/kg, and 4 mg/kg, while rivastigmine (2 mg/kg) was used as reference standard drug. Cognitive dysfunction induced by STZ was assessed by behavioral tests like Morris water maze and novel object recognition test. **Treatment with CrPic revealed attenuation of cognitive deficit.**

https://pubmed.ncbi.nlm.nih.gov/35829940/ Trivalent chromium supplementation ameliorates adjuvant induced rheumatoid arthritis through up-regulation of FOXP3 and decrease in synovial Cathepsin G expression 2022

Adult male albino rats were randomly divided into **four groups: normal, untreated RA, prednisolone treated RA (1.25 mg/kg/day) and Cr (III) treated RA groups (80 µg/kg/day)**, induction of RA was done by subcutaneous complete Freund adjuvant injection. Study duration was 4 weeks throughout which arthritis scoring and weight measurement were pursued. Histopathological examination and immunohistochemical FOXP3 assessment were done for joint biopsies. Serum inflammatory markers (interleukin 17, interleukin 10, CRP) and synovial erosive arthritis marker (Cathepsin G) were measured. HDL and non-HDL cholesterol were estimated as well.

Results: Cr (III) treatment showed marked clinical and histopathological improvement, also astonishing anti-inflammatory effects (increase in FOXP3 expression and interleukin 10, with decrease in interleukin 17, CRP and synovial Cathepsin G) to the extent that Cr (III) effects on inflammation abolishment were comparable to that of prednisolone and even better at some aspects. Moreover, Cr (III) was protective from side effects, i.e., weight gain and dyslipidemia that were seen with prednisolone treatment.

https://pubmed.ncbi.nlm.nih.gov/35742553/ Alzheimer's Disease Association with Metals and Metalloids Concentration in Blood and Urine. 2022

As there is some evidence that the risk for Alzheimer's disease (AD) is partially attributable to environmental exposure to some metals and metalloids, we examined an association between AD and arsenic, chromium, and selenium in 53 AD patients and 217 controls. **In AD patients, urinary arsenic and blood chromium were significantly higher, while blood selenium was significantly lower compared to controls.**

https://clinicaltrials.gov/ct2/show/NCT03038282 Effects of Chromium on Insulin Resistance in Alzheimer Disease Patients

Chromium is an essential nutrient required for optimal insulin activity and normal carbohydrate and lipid metabolism. Beyond its nutritional effects, **dietary supplement of chromium causes beneficial outcomes against several diseases, in particular diabetes-associated complications such as Alzheimer Disease.** Common forms include chromium chloride, chromium nicotinate, and chromium picolinate. The argument for chromium supplementation relies on evidence from case reports of resolution of diabetic symptoms refractory to insulin via chromium added to total parenteral nutrition, and experiments in which animals deficient in chromium exhibited impaired glucose metabolism.

https://pubmed.ncbi.nlm.nih.gov/20423560/ Improved cognitive-cerebral function in older adults with chromium supplementation 2010

Insulin resistance is implicated in the pathophysiological changes associated with Alzheimer's disease, and pharmaceutical treatments that overcome insulin resistance improve memory function in subjects with mild cognitive impairment (MCI) and early Alzheimer's disease. Chromium (Cr) supplementation improves glucose disposal in patients with insulin resistance and diabetes. We sought to assess whether supplementation with **Cr might improve memory and neural function in older adults with cognitive decline**. In a placebo-controlled, double-blind trial, we randomly assigned 26 older adults to receive either chromium picolinate (CrPic) or placebo for 12 weeks. Memory and depression were assessed prior to treatment initiation and during the final week of treatment. We also performed functional magnetic resonance imaging (fMRI) scans on a subset of subjects. Although learning rate and retention were not enhanced by CrPic supplementation, **we observed reduced semantic interference on learning, recall, and recognition memory tasks.** In addition, **fMRI indicated comparatively increased activation for the CrPic subjects in right thalamic, right temporal, right posterior parietal, and bifrontal regions.** These findings **suggest that supplementation with CrPic can enhance cognitive inhibitory control and cerebral function in older adults at risk for neurodegeneration.**

Copper (requires homeostatis)

Sources: Beef,liver,Oysters,Baking Chocolate, Pototoes, Mushrooms, Cashews, Sunflour Seeds, Turkey, Salmon

RDA: 900mcg (average intake is 1100-1400mcg) ie deficiency rare

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3227474/ Disturbed Copper Bioavailability in Alzheimer's Disease

Copper is needed by every oxygen-requiring cell and can be **toxic in excess**. It is an essential metal with extremely complex roles in numerous different biological functions from acute phase reactant to mitochondrial energy generation. Cu levels are very tightly regulated on the level of duodenal absorption as well as uptake into cells or excretion from cells. **Copper promotes the non-amyloidogenic processing of APP and thereby lowers the Aβ production in cell culture systems, and it increases lifetime and decreases soluble amyloid production in APP transgenic mice. In a clinical trial with Alzheimer patients, the decline of Aβ levels in CSF, which is a diagnostic marker, is diminished in the verum group (8 mg copper/day), indicating a beneficial effect of the copper treatment.**

A possible role of Cu in AD has remained a contentious topic during the past 15 years, as has been the question whether extracellular amyloid deposited in plaques is the causative agent in AD. The scientific community was divided as to whether Cu has a role at all, and—if yes—whether it is friend or foe. The Cu-clinical trial demonstrates that long-term oral intake of 8 mg Cu (Cu-(II)-orotate-dihydrate) can be excluded as a risk factor for AD, and—based on the CSF biomarker analysis—that **Cu may potentially play a beneficial role in this disease.**

https://pubmed.ncbi.nlm.nih.gov/17300982/ Copper and Alzheimer's disease 2007

Copper is essential for some of the enzymes that have a role in brain metabolism. Sophisticated mechanisms balance copper import and export to **ensure proper nutrient levels (homeostasis) while minimizing toxic effects**. Several neurodegenerative diseases including Alzheimer's disease (**AD) are characterized by modified copper homeostasis**. This change seems to contribute either directly or indirectly to increased oxidative stress, an important factor in neuronal toxicity. When coupled to misfolded proteins, this modified copper homeostasis appears to be an important factor in the pathological progression of AD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9372870/pdf/WJCC-10-7631.pdf Role of micronutrients in Alzheimer's disease: Review of available evidence 2020

Copper is a ubiquitous element. Red meat, nuts, and vegetables are rich sources of copper. Copper is one of the most abundant transition metals in the human body. It is involved in collagen synthesis, antioxidant defense, skin pigmentation, neurotransmitter synthesis, and iron homeostasis[13]. Thus, it plays an important role in human physiology. **Copper is closely related to AD**[14,15]. The most common neuropathic lesions in AD are plaques of neurofibrillary tangle, amyloid, and soluble oligomers with **large amounts of copper at their core. Patients with AD were shown to have significantly higher levels of copper in their brain tissue than the general population**, which promotes the formation of neurofibrillary tangle, amyloid, and other proteins [16-18]. Copper promotes the neurofibrillary tangle of hyperphosphorylation Tau, which aggravates homeostatic disorders; in addition, copper promotes oxidative stress, which has been observed in the brain tissue of many patients with AD[19]. **Rosmarinic acid is a commonly used anti-AD drug. Rosmarinic acid has been shown to reduce copper-induced neurotoxicity** due to its antioxidant effect in vitro and in vivo, by preventing the binding of amyloid protein with copper[20]. The properties of copper-bound amyloid proteins have been employed for auxiliary positron emission tomography in the diagnosis of AD in mouse models[21]. Detection of copper is useful in the diagnosis and prevention of AD[22,23]. In addition, **long-term exposure to copper is associated with cognitive decline** and microglia degeneration[24]. TDMQ20 was shown to reduce the copper content in the cerebral cortex of mice[25], and ameliorate oxidative stress in the cerebral cortex of mice, further attenuating the neurotoxicity of amyloid[26]. High affinity **metal ion chelating agents such as chitosan can be an effective treatment for AD**. The therapeutic effect of **chitosan is related to its ability to absorb copper ions[27**

https://pubmed.ncbi.nlm.nih.gov/28889269/ Copper and Alzheimer's Disease 2017

major changes in copper (Cu) levels and localisation have been identified in AD brain, with accumulation of Cu in amyloid deposits, together with deficiency of Cu in some brain regions. The amyloid precursor protein (APP) and the amyloid beta (Aβ) peptide both have Cu binding sites, and interaction with Cu can lead to potentially neurotoxic outcomes through generation of reactive oxygen species. In addition, **AD patients have systemic changes to Cu metabolism, and altered Cu may also affect neuroinflammatory outcomes in AD**. Although we still have much to learn about **Cu homeostasis in AD** patients and its role in disease aetiopathology, therapeutic approaches for regulating Cu levels and interactions with Cu-binding proteins in the brain are currently being developed. This review will examine how Cu is associated with pathological changes in the AD brain and how these may be targeted for therapeutic intervention.

https://pubmed.ncbi.nlm.nih.gov/21714485/ The heterogeneous nature of Cu2+ interactions with Alzheimer's amyloid-β peptide 2011

Within the brain, senile plaques, which comprise extracellular deposits of the amyloid-β peptide (Aβ), are the most common pathological feature of AD. A **high concentration of Cu(2+) is** found within these plaques, which are also areas under oxidative stress. Laboratory work has shown that in vitro Aβ will react with Cu(2+) to induce peptide aggregation and the production of reactive oxygen species. As such, this interaction offers a possible explanation for two of the defining pathological features observed in the AD brain: the presence of amyloid plaques, which consist largely of insoluble Aβ aggregates, and the abundant oxidative stress therein. Researchers have accordingly **put forth the "metals hypothesis" of AD**, which postulates that compounds designed to inhibit Cu(2+)/Aβ interactions and redistribute Cu(2+) may offer therapeutic potential for treating AD.

https://pubmed.ncbi.nlm.nih.gov/34878720/ Rational Design of a Cu Chelator That Mitigates Cu-Induced ROS Production by Amyloid Beta 2022

Alzheimer's disease severely perturbs transition metal homeostasis in the brain leading to the accumulation of excess metals in extracellular and intraneuronal locations. The amyloid beta protein binds these transition metals, ultimately causing severe oxidative stress in the brain. **Metal chelation therapy** is an approach to sequester metals from amyloid beta and relieve the oxidative

stress. Here we have designed a mixed N/O donor Cu chelator inspired by the proposed ligand set of Cu in amyloid beta. We demonstrate that the chelator effectively removes Cu from amyloid beta and suppresses reactive oxygen species (ROS) production by redox silencing and radical scavenging both in vitro and in cellulo.
https://pubmed.ncbi.nlm.nih.gov/35043280/ Blood copper excess is associated with mild cognitive impairment in elderly Chinese 2022
Results: A total of 1057 subjects with an average age of 71.82 ± 6.45 years were included in this study. There were 215 patients with MCI, and the prevalence of MCI was 20.34%. After adjusting for general demographic variables, logistic regression analysis showed that the **risk of MCI in the elderly with high copper level was 1.354 times higher than that in the elderly with low copper level** (OR 1.354, 95% CI 1.047-1.983, P = 0.034).
https://pubmed.ncbi.nlm.nih.gov/31786641/ Changes of trace element status during aging: results of the EPIC-Potsdam cohort study 2020
Conclusions: In conclusion, in this population-based study of healthy elderly, decrease in Mn, Zn, and Se concentrations and increase in Fe, Cu, and I concentrations were observed over 20 years of follow-up. Further research is required to investigate dietary determinants and markers of TE status as well as the relationships between TE profiles and the risk of age-related diseases.

Iron (iron dyshomeostasus, ferroptosis, --see glutathione peroxidase 4 (Gpx4) for prevention?)

https://pubmed.ncbi.nlm.nih.gov/29865061/ Iron and Alzheimer's Disease: An Update on Emerging Mechanisms 2018
Iron is a crucial transition metal for life and is the most abundant transition metal in the brain. However, iron's biological utility as an effective redox cycling metal also endows it with the potential to catalyze production of noxious free radicals. This "Janus-faced" nature of iron demands a **tight regulation of cellular its metabolism**. Aberrations in brain iron homeostasis can elevate levels of this **redox-active metal, leading to mislocalization of the metal and catastrophic oxidative damage to sensitive cellular and subcellular structures.** **Iron dyshomeostasis has been strongly linked to the pathogenesis of Alzheimer's disease (AD)**, as well as other major neurodegenerative diseases. Targeting iron dyshomeostasis in the brain represents a rational approach to treat the underlying disease.
https://pubmed.ncbi.nlm.nih.gov/35391749/ Iron Dyshomeostasis and Ferroptosis: A New Alzheimer's Disease Hypothesis? 2022
Iron plays a crucial role in many physiological processes of the human body, but **iron is continuously deposited in the brain as we age**. Early studies found **iron overload is directly proportional to cognitive decline** in Alzheimer's disease (AD). Amyloid precursor protein (APP) and tau protein, both of which are related to the AD pathogenesis, are associated with brain iron metabolism. A variety of iron metabolism-related proteins have been found to be abnormally expressed in the brains of AD patients and mouse models, resulting in iron deposition and promoting AD progression.
https://pubmed.ncbi.nlm.nih.gov/36188557/ Iron dyshomeostasis and ferroptosis in Alzheimer's disease: Molecular mechanisms of cell death and novel therapeutic drugs and targets for AD 2022
Alzheimer's disease (AD) is a degenerative disease of the central nervous system that is the most common type of senile dementia. **Ferroptosis is a new type of iron-dependent programmed cell death** identified in recent years that is different from other cell death forms. Ferroptosis is induced by excessive accumulation of lipid peroxides and reactive oxygen species (ROS) in cells. In recent years, it has been found that **ferroptosis plays an important role in the pathological process of AD**. Iron dyshomeostasis contribute to senile plaques (SP) deposition and neurofibrillary tangles (NFTs). Here, we review the potential interaction between AD and ferroptosis and the major pathways regulating ferroptosis in AD. We also review the active natural and synthetic compounds such as iron chelators, lipid peroxidation inhibitors and antioxidants available to **treat AD by alleviating iron dyshomeostasis and preventing ferroptosis** in mice and cell models to provide valuable information for the future treatment and prevention of AD.
https://pubmed.ncbi.nlm.nih.gov/34422824/ Ferroptosis, a Potential Therapeutic Target in Alzheimer's Disease
review the **application of ferroptosis inhibitors in both AD** clinical trials and mice/cell models, to provide valuable information for future treatment and prevention of this devastating disease.
https://pubmed.ncbi.nlm.nih.gov/27506793/ Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis 2016
we found that PUFA oxidation by lipoxygenases via a PHKG2-dependent iron pool is necessary for ferroptosis and that the covalent inhibition of the catalytic selenocysteine in Gpx4 prevents **elimination of PUFA hydroperoxides**; these findings suggest new strategies for controlling ferroptosis in diverse contexts.
https://pubmed.ncbi.nlm.nih.gov/29795546/ Unsolved mysteries: How does lipid peroxidation cause ferroptosis? 2018
Ferroptosis is a cell death process driven by damage to cell membranes and linked to numerous human diseases. **Ferroptosis is caused by loss of activity of the key enzyme that is tasked with repairing oxidative damage to cell membranes-glutathione peroxidase 4 (GPX4).** GPX4 normally removes the dangerous products of iron-dependent lipid peroxidation, protecting cell membranes from this type of damage; when GPX4 fails, ferroptosis ensues.
https://pubmed.ncbi.nlm.nih.gov/26653790/ Ferroptosis: Death by Lipid Peroxidation 2016
Ferroptosis is a regulated form of cell death driven by loss of activity of the lipid repair enzyme glutathione peroxidase 4 (GPX4) and subsequent accumulation of lipid-based reactive oxygen species (ROS), particularly lipid hydroperoxides.
https://pubmed.ncbi.nlm.nih.gov/36090039/ The mechanisms of ferroptosis and its role in alzheimer's disease 2022
The ferroptosis pathways within nerve cells include iron homeostasis regulation, cystine/glutamate (Glu) reverse transporter (system xc^-), **glutathione (GSH)/glutathione peroxidase 4 (GPX4)**, and lipid peroxidation. In the regulation pathway of AD iron homeostasis, abnormal iron uptake, excretion and storage in nerve cells lead to increased intracellular free iron and Fenton reactions. Furthermore, decreased Glu transporter expression leads to Glu accumulation outside nerve cells, resulting in the inhibition of the system xc^- pathway. **GSH depletion causes abnormalities in GPX4, leading to excessive accumulation of lipid peroxides.** Alterations in these specific pathways and amino acid metabolism eventually lead to ferroptosis. This review explores the connection between AD and the ferroptosis signaling pathways and amino acid metabolism, potentially informing future AD diagnosis and treatment methodologies.
https://pubmed.ncbi.nlm.nih.gov/32199332/ Iron dyshomeostasis, lipid peroxidation and perturbed expression of cystine/glutamate antiporter in Alzheimer's disease: Evidence of ferroptosis 2020
Iron dyshomeostasis is implicated in Alzheimer's disease (AD) alongside β-amyloid and tau pathologies. Despite the recent discovery of ferroptosis, an iron-dependent form cell death, hitherto, in vivo evidence of ferroptosis in AD is lacking. The present study uniquely adopts an integrated multi-disciplinary approach, combining protein (Western blot) and elemental analysis (total reflection X-ray fluorescence) with metabolomics (^{1}H nuclear magnetic resonance spectroscopy) to identify iron dyshomeostasis and ferroptosis, and possible novel interactions with metabolic dysfunction in age-matched male cognitively normal (CN) and AD post-mortem brain tissue (n = 7/group). Statistical analysis was used to compute differences between CN and AD, and to examine associations between proteins, elements and/or metabolites. **Iron dyshomeostasis with elevated levels of ferritin, in the absence of increased elemental iron, was observed in AD.** Moreover, AD was characterised by enhanced expression of the light-chain subunit of the cystine/glutamate transporter (xCT) and lipid peroxidation, reminiscent of ferroptosis, alongside an augmented excitatory glutamate to inhibitory GABA ratio. Protein, element and metabolite associations also greatly differed between CN and AD suggesting widespread metabolic dysregulation in AD. We demonstrate iron dyshomeostasis, upregulated xCT (impaired glutathione metabolism) and lipid peroxidation in AD, **suggesting anti-ferroptotic therapies may be efficacious in AD.**
https://pubmed.ncbi.nlm.nih.gov/32760266/ Spotlight on Ferroptosis: Iron-Dependent Cell Death in Alzheimer's Disease 2020
Iron appears to be the common theme prevalent across neurodegenerative diseases. Iron has been shown to promote aggregation and pathogenicity of the characteristic aberrant proteins, β-amyloid, tau, α-synuclein, and TDP43, in these diseases. Further support for the involvement of iron in pathogenesis is provided by the recent discovery of a new form of cell death, **ferroptosis.** Arising from iron-dependent lipid peroxidation, **ferroptosis is augmented in conditions of cysteine deficiency and glutathione peroxidase-4 inactivation.** Here, we review clinical trials that provide the rationale for targeting ferroptosis to delay the pathogenesis of Alzheimer's disease (AD), potentially of relevance to other neurodegenerative diseases.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9372870/pdf/WJCC-10-7631.pdf Role of micronutrients in Alzheimer's disease: Review of available evidence 2022
Iron is one of the essential trace metal elements which is widely distributed in the human body. Iron is involved in material transportation, growth and development, cell differentiation, gene expression, and lipid peroxidation. Abnormal heme content and deranged iron homeostasis are more common in AD [49]. Accumulation of iron in the brain is a common phenomenon in many neurodegenerative disorders. Postmortem studies have documented markedly increased concentration of ferritin and hemosiderin aggregates in the brain tissues of patients with severe AD[50]. Inadequate iron intake during pregnancy may cause iron deficiency in fetal brain tissue, increasing the risk of neurological defects. With the increase in age, accumulation of iron in brain tissue can also occur because of brain tissue-amyloid protein deposition and plaque, which in turn promotes further iron deposition[51]. A **growing body of evidence suggests that iron dysregulation in brain neurons plays a key role in AD [52]**. Studies have documented high iron concentrations in deep gray matter structures of brain tissue in patients with AD[53]. Iron deposition promotes increased Tau levels in brain tissue and neurofibrillary Tangle Tau formation[10,54]. Iron also accelerates the deposition of amyloid proteins in brain tissue[55]. Increased concentration of iron-rich pollutants in the air predisposes people to AD[56]. Studies have shown that-amyloid precursor protein can be hydrolyzed to-amyloid, which is dependent on iron transporter transmembrane transport[57]. CISD2 gene encodes CDGSH FT-DOMAIN Protein 2, and up-regulation of CDGSH FT-DOMAIN PROTEIN 2 can improve mitochondrial structure and synaptic function, which plays a neuroprotective role[58]. **Research has shown that oxidative stress promotes iron deposition in brain tissue**, which plays an important role in the development of AD. In a study, scanning electron microscope and transmission electron microscope were used to examine specific iron-rich areas in the hippocampus of anatomical specimens of brain tissue from patients with AD. The authors found a significant increase in both Tau and amyloid proteins in brain tissue, which suggests that the effect of oxidative stress on AD is related to the oxidation of iron[59]. Endothelial cells in brain tissue can promote the formation of new blood vessels in the environment of embryonic development, and they rely on specific metabolic pathways to achieve different cellular functions. Pilin-1, a transmembrane protein of endothelial cells, regulates mitochondrial function and iron homeostasis, thus affecting the development of AD[60]. **Use of iron chelating agents such as desfer-rioxamine mesylate (desferrioxamine) was shown to reduce the iron content in brain tissue in animal models of AD.** This effect was related to the ease with which desferrioxamine crosses the blood brain barrier[61]. Multi-functional nanoparticles w20xd4-spions may contribute to the diagnosis and treatment of AD. This is related to the ability of multi-functional nanoparticles w20xd4-spions to readily cross the blood-brain barrier and enhance microglia phagocytosis[62]. Iron oxide nanoparticles have been used in clinical studies to improve AD, owing to their ability to cross the blood-brain barrier[63]. Iron deposition is a pathway that **regulates cell death, initiated by glutathione and lipid peroxidation signals** [64]. Ferroptosis, a recently discovered form of cell death caused by accumulation of byproducts of lipid peroxidation, is also involved in the pathogenesis of AD. **Excess iron was shown to exacerbate oxidative damage and cognitive deficit in a mouse model of AD**. Use of specific iron deposition inhibitors was

shown to alleviate the degree of neuronal death and memory damage in mice, especially in the hippocampus[65]. **Brain iron metabolism disorder is one of the main characteristics of AD.** Hemagglutinin neutralizes heme toxicity, maintains iron homeostasis, enhances antioxidant capacity by breaking down metabolites, biliverdin and carbon monoxide, and alleviates iron-mediated lipid peroxidation, which improves hippocampal volume, metabolism, and cognitive function in patientswith AD[66].

https://pubmed.ncbi.nlm.nih.gov/1749542/ The influence of tea on iron and aluminum bioavailability in the rat 1991

The aluminum from tea or tea leaves was very poorly absorbed by young, growing rats. **Tea had a decidedly adverse effect on the animals' iron status.**

https://pubmed.ncbi.nlm.nih.gov/11029010/ Effect of tea and other dietary factors on iron absorption 2000

Iron deficiency is a major world health problem, that is, to a great extent, caused by poor iron absorption from the diet. Several dietary factors can influence this absorption. Absorption enhancing factors are ascorbic acid and meat, fish and poultry; i**nhibiting factors are plant components in vegetables, tea and coffee** (e.g., polyphenols, phytates), and calcium.

From these calculations we conclude that the presence of **sufficient amounts of iron absorption enhancers (ascorbic acid, meat, fish, poultry, as present in most industrialized countries) overcomes inhibition of iron absorption from even large amounts of tea.**

https://www.healthline.com/health/sodium-phosphate#foods-withsodium-phosphate Foods that contain sodium phosphate

Foods with naturally occurring sodium phosphate include: nuts and legumes, meat,fish, poultry, eggs

Foods that may have added sodium phosphate include: cured meat, deli meat, fast food, processed foods, commercially prepared baked goods and cake mixes, canned tuna

https://pubmed.ncbi.nlm.nih.gov/31786641/ Changes of trace element status during aging: results of the EPIC-Potsdam cohort study 2020

Conclusions: In conclusion, in this population-based study of healthy elderly, decrease in Mn, Zn, and Se concentrations and increase in Fe, Cu, and I concentrations were observed over 20 years of follow-up. Further research is required to investigate dietary determinants and markers of TE status as well as the relationships between TE profiles and the risk of age-related diseases.

Iron chelating (see curcumin, Mucuna pruiens , tea, grape, wine, fruits&nuts[Quercetin])

https://pubmed.ncbi.nlm.nih.gov/35624729/ Role of Iron in Aging Related Diseases 2022

Iron progressively accumulates with age and can be further exacerbated by dietary iron intake, genetic factors, and repeated blood transfusions. While iron plays a vital role in various physiological processes within the human body, its accumulation contributes to cellular aging in several species. In its free form, iron can initiate the formation of free radicals at a cellular level and contribute to systemic disorders. This is most evident in high iron conditions such as hereditary hemochromatosis, when accumulation of iron contributes to the development of arthritis, cirrhosis, or cardiomyopathy. A growing body of research has further identified iron's contributory effects in neurodegenerative diseases, ocular disorders, cancer, diabetes, endocrine dysfunction, and cardiovascular diseases. Reducing iron levels by repeated phlebotomy, iron chelation, and dietary restriction are the common therapeutic considerations to prevent iron toxicity. **Chelators such as deferoxamine, deferiprone, and deferasirox have become the standard of care in managing iron overload** conditions with other potential applications in cancer and cardiotoxicity. In certain animal models, drugs with iron chelating ability have been found to promote health and even extend lifespan. As we further explore the role of iron in the aging process, iron chelators will likely play an increasingly important role in our health.

https://pubmed.ncbi.nlm.nih.gov/25005181/ Iron chelating strategies in systemic metal overload, neurodegeneration and cancer 2014

Disturbances of iron homeostasis and an increase in its level may lead to overload and neurodegenerative diseases. **Phlebotomy** was for a long time the only way of removing excess iron. But since there are many possible disadvantages of this method, chelation therapy seems to be a logical approach to remove toxic levels of iron. In clinical use, there are three drugs: desferrioxamine, deferiprone and deferasirox. FBS0701, a novel oral iron chelator, is under clinical trials with very promising results. Developing novel iron-binding chelators is an urgent matter, not only for systemic iron overload, but also for neurodegenerative disorders, such as Parkinson's disease. **Deferiprone is also used in clinical trials in Parkinson's disease**. In neurodegenerative disorders the main goal is not only to remove iron from brain tissues, but also its redistribution in system. Few chelators are tested for their potential use in neurodegeneration, such as nonhalogeneted derivatives of clioquinol. Such compounds gave promising results in animal models of neurodegenerative diseases. Drugs of possible use in neurodegeneration must meet certain criteria. Their development includes the improvement in blood brain barrier permeability, low toxicity and the ability to prevent lipid peroxidation. One of the compounds satisfying these requirements is VK28. In rat models it was able to protect neurons in very low doses without significantly changing the iron level in liver or serum. Also iron chelators able to regulate activity of monoamine oxidase were tested. Polyphenols and flavonoids are able to prevent lipid peroxidation and demonstrate neuroprotective activity. While cancer does not involve true iron overload, neoplastic cells have a higher iron requirement and are especially prone to its depletion. It was shown, that desferrioxamine and deferasirox are antiproliferative agents active in several types of cancer. Very potent compounds with possible use as anticancer drugs are thiosemicarbazones. They are able to inhibit ribonucleotide reductase, an enzyme involved in DNA synthesis. Because the relationship between the development of overload / neurodegenerative disorders, or cancer, and iron are very complex, comprehension of the mechanisms involved in the regulation of iron homeostasis is a crucial factor in the development of new pharmacological strategies based on iron chelation. **In view of various factors closely involved in pathogenesis of such diseases, designing multifunctional metal-chelators seems to be the most promising approach,** but it requires a lot of effort. In this perspective, the review summarizes systemic iron homeostasis, and in brain and cancer cells, iron dysregulation in neurodegenerative disease and possible chelation strategies in the treatment of metal systemic overload, neurodegeneration and cancer.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3821171/ Synthetic and natural iron chelators 2009

The chemical properties of curcumin are consistent with iron-chelator activity [171], and our laboratory recently observed that liver cells treated with curcumin exhibited hallmarks of iron depletion, which included decreases in the iron-storage protein ferritin, increases in TfR1 and activation of iron-regulatory proteins [172]. **Curcumin also acts as an iron chelator** in vivo, particularly in the setting of mild iron deficiency [170,172]. Under these conditions, dietary curcumin exerted profound effects on systemic iron, inducing a decline in hematocrit, hemoglobin, serum iron and Tf saturation, the appearance of hypochromic red blood cells and decreases in spleen and liver iron content [170]. Curcumin also repressed synthesis of hepcidin, a peptide that plays a central role in regulation of systemic iron balance [170]. Consistent with these reports, curcumin reduced NTBI in a mouse model of β-thalassemia [173]

Kolaviron, a natural biflavonoid from Garcinia kola seeds that have been used in African herbal medicine, was shown to protect against oxidation of lipoproteins in rats through the **chelating activity of kolaviron on Fe2+**

Pycnogenol™ (PYC), a standardized extract composed of a mixture of flavonoids, mainly procyanidins and phenolic acids obtained from a French maritime pine, may be shown to provide cardioprotective activity, which has been attributed to the strong free radical scavenging activity of its oligomeric procyanidin components [183]. Procyanidins extracted from Vitis vinifera, which have a composition similar to that of PYC, were observed to **form a complex with ferric iron** with a procyanidin–iron ratio of 1:2 [184]. Furthermore, the stability constant of the **procyanidin–iron complex was comparable to another strong iron-chelating agent, nitrilotriacetate** (NTA)

Baicalein and its glycoside baicalin, the major bioactive compounds found in the Chinese herb Scutellaria baicalensis Georgi, have been found to **strongly inhibit iron-promoted Fenton chemistry** via a combination of chelation and radical scavenging mechanisms [186] **Baicalin and quercetin** (see later) were shown to increase antioxidant status and **decrease iron content** and lipid peroxidation in the liver of mice with iron-overload-induced liver oxidative injury [189,190].

Grape, wine, fruits & nuts—The iron-binding properties of the flavonol **quercetin**, the major phenolic phytochemical present in cranberries and other selected phenolic compounds (chrysin, 3-hydroxyflavone, 3′,4′-dihydroxy flavone, rutin and flavones), were investigated in aqueous media using UV/vis, NMR and electron paramagnetic resonance (EPR) spectropscopies and ESI–MS [191]. **Quercetin was found to bind Fe^{2+} more strongly** than the well-known Fe^{2+} chelator ferrozine. Quercetin can also bind Fe^{3+}, Ga^{3+} and Zn^{2+}. Interestingly, quercetin completely suppressed iron-promoted Fenton chemistry at micromolar levels, even in the presence of the major cellular iron chelators ATP or citrate.

Grape seed extract (GSE) contains various polyphenols, including gallic acid, catechin, epigallocatechin gallate (EGCG) and proanthocyanidins. GSE possesses antioxidant activity [202–205], which derives from the ability of these constituents to scavenge free radicals and to **chelate metals such as iron** [204]. Interestingly, GSE and EGCG inhibited nonheme iron absorption in human intestinal Caco-2 cells by reducing basolateral iron exit via FPN-1 rather than by decreasing apical iron import [204]. A study of brain cell iron chelation suggested that EGCG and GSE are membrane permeable and may enter cells as complex forms with Fe^{2+} [206]. **The iron-chelating activity of EGCG(ingredient of GSE) was comparable with that of DFO** [206].

Green tea catechins & black tea theaflavins—Flavonoids extracted from tea leaves (catechins present in green teas and theaflavins present in black teas) act directly as radical scavengers and exert indirect antioxidant effects through activation of transcription factors and antioxidant enzymes [175,207]. The most abundant polyphenolic compound of green tea is **EGCG** [175].

Soy protein. Consumption of commercially prepared powders of soy protein with native phytate after only 6 weeks was shown to **reduce iron stores**, as assessed by serum ferritin concentrations, in postmenopausal women [230]

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3654245/ Chelation: Harnessing and Enhancing Heavy Metal Detoxification—A Review 2013

Metal binding proteins, including **metallothioneins**, are potent chelators for heavy metals and are central to the natural response of the body to these toxic elements [27, 28]. **Glutathione** is another potent chelator involved in cellular response, transport, and excretion of metal cations and is a biomarker for toxic metal overload [29–31].

(i) **Taurine** [49–51] and **methionine** [52] are sulphur-containing amino acids. They are rich in membranes particularly of excitable tissues, and they decrease oxidative stress markers resulting from heavy metal exposure.

(ii) **Alpha lipoic acid** is a powerful antioxidant that regenerates other antioxidants (e.g., vitamins E and C, and reduced glutathione) and has metal-chelating activity. Both fat and water soluble, it is readily absorbed from the gut and crosses cellular and blood-brain membrane barriers [22, 53]. Clinical experience is that it must be used carefully as it poses particular risks of redistribution of metals.

(iii) **N-acetyl-cysteine (NAC)**, an orally available precursor of cysteine, is a chelator of toxic elements and may stimulate glutathione synthesis, particularly in the presence of vitamins C and E [54–56].

lithium(not official micronutrient)

Sources: Cereals, Potatoes, Tomatoes, Cabbage, Nutmeg, Black and Green Tea (note highly dependent on soil conditions)
RDA: 1000mcg
https://pubmed.ncbi.nlm.nih.gov/31156173/ Lithium as a Treatment for Alzheimer's Disease: The Systems Pharmacology Perspective
Lithium chloride, a pharmacological compound approved for the therapy of psychiatric disorders, represents a **poorly explored compound for the treatment of Alzheimer's disease (AD)**. Lithium has been shown to reduce downstream effects associated with the aberrant overactivation of certain molecular pathways, such as glycogen synthase kinase 3 subunit β (GSK3-β)-related pathways, involved in AD-related pathophysiology. I
https://pubmed.ncbi.nlm.nih.gov/26402004/ Lithium as a Treatment for Alzheimer's Disease: A Systematic Review and Meta-Analysis
Three clinical trials including 232 participants that met the study's inclusion criteria were identified. **Lithium significantly decreased cognitive decline as compared to placebo** (standardized mean difference = -0.41, 95% confidence interval = -0.81 to -0.02, p = 0.04, I2 = 47% , 3 studies, n = 199). There were no significant differences in the rate of attrition, discontinuation due to all causes or adverse events, or CSF biomarkers between treatment groups.
Conclusions: The results indicate that **lithium treatment may have beneficial effects on cognitive performance in subjects with MCI and AD dementia**.
https://journalbipolardisorders.springeropen.com/articles/10.1186/s40345-020-00188-z Low-dose lithium against dementia
As far as I can tell, however, the study by Forlenza and co-workers is the first low-dose lithium (0.25–0.5 mmol/l) trial in MCI, and it is certainly a remarkable feat to conduct such a study over 4 years. This is why it is justified not to dismiss this work. In taking a closer look it appears the effect sizes are quite strong: **A relative risk of 0.54 [95%-CI 0.20–1.42] of transitioning to dementia after 4 years**, albeit under the assumption that none of the drop-outs became demented.
https://pubmed.ncbi.nlm.nih.gov/22746245/ Microdose lithium treatment stabilized cognitive impairment in patients with Alzheimer's disease 2013
A **lower incidence of dementia in bipolar patients treated with lithium** has been described. This metal inhibits the phosphorylation of glycogen-synthase-kinase 3-α and β, which are related to amyloid precursor protein processing and tau hyperphosphorylation in pathological conditions, respectively. Following the same rationale, a group just found that lithium has disease-modifying properties in amnestic mild cognitive impairment with potential clinical implications for the prevention of Alzheimer's Disease (AD) when a dose ranging from **150 to 600 mg** is used. As l**ithium is highly toxic in regular doses**, our group evaluated the **effect of a microdose of 300 µg**, administered once daily on AD patients for 15 months. In the evaluation phase, the treated group showed **no decreased performance in the mini-mental state examination test,** in opposition to the lower scores observed for the control group during the treatment, with significant differences starting three months after the beginning of the treatment, and increasing progressively. This data suggests the **efficacy of a microdose lithium treatment in preventing cognitive loss, reinforcing its therapeutic potential to treat AD using very low doses.**
https://wwww.unboundmedicine.com/medline/citation/29859917/Lithium_Treatment_for_Agitation_in_Alzheimer's_disease__Lit_AD_:_Clinical_rationale_and_study_design_ 2018
Lithium is an established treatment for bipolar and other psychotic disorders in which agitation can occur. The Lit-AD study is the first randomized, double-blind, placebo-controlled trial to assess the **efficacy of lithium treatment for symptoms of agitation or aggression**, with or without psychosis, in older adults diagnosed with AD. Patients are randomly assigned to low dose (150-600 mg) lithium or placebo, targeting a blood level of 0.2-0.6 mmol/L, stratified by the presence/absence of psychotic symptoms. TRIAL IN PROGRESS
https://www.cambridge.org/core/journals/the-british-journal-of-psychiatry/article/lithium-and-risk-for-alzheimers-disease-in-elderly-patients-with-bipolar-disorder/2F966D8BD1FF7E946C95949950AA61C1 2018
It thus seems possible that a **protective effect of lithium against Alzheimer's disease** in patients with bipolar disorder might be a result of its intrinsic biological properties in the brain.

Magnesium

Sources: Green Leafy Vegs, spinach, nuts, whole grains, Pumpkin seeds(156mg/1ounce),Almonds(80mg/ounce),Salmon(26mg),Banana(32mg)
RDI: 420mg/day male, 320mg/day female
https://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/ Magnesium
Magnesium, an abundant mineral in the body, is naturally present in many foods, added to other food products, available as a dietary supplement, and present in some medicines (such as antacids and laxatives). Magnesium is a **cofactor in more than 300 enzyme systems** that regulate diverse biochemical reactions in the body, including protein synthesis, muscle and nerve function, blood glucose control, and blood pressure regulation [1-3]. Magnesium is required for energy production, oxidative phosphorylation, and glycolysis. It contributes to the structural development of bone and is required for the synthesis of DNA, RNA, and the antioxidant glutathione. Magnesium also plays a role in the active transport of calcium and potassium ions across cell membranes, a process that is important to nerve impulse conduction, muscle contraction, and normal heart rhythm [3].
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5988891/ Magnesium Ions Inhibit the Expression of Tumor Necrosis Factor α and the Activity of γ-Secretase in a β-Amyloid Protein-Dependent Mechanism in APP/PS1 Transgenic Mice 2018
Recently, AD was found to be associated with magnesium ion (Mg^{2+}) deficit and tumor necrosis factor-alpha (TNF-α) elevation in the serum or brains of AD patients.
https://pubmed.ncbi.nlm.nih.gov/26351088/ Magnesium Status in Alzheimer's Disease: A Systematic Review 2016
The interest in **poor magnesium (Mg) status as risk factor for Alzheimer's disease (AD) is increasing due to its antioxidant and neuroprotective properties.** A systematic PubMed literature search of studies investigating Mg status was undertaken comparing AD to healthy controls (HCs) or patients with medical illness (medical controls [MCs]). Standardized mean differences (SMDs) ± 95% confidence intervals (CIs) were calculated for all outcomes. Of 192 potentially eligible studies, 13 were included (559 patients with AD, 381 HCs, and 126 MCs). Compared to HCs, patients with **AD had significantly lower Mg in cerebrospinal fluid** (2 studies; SMD = -0.35;P= .02) and in hair (2 studies; SMD = -0.75;P= .0001). No differences between AD and controls were evident for serum Mg. In conclusion, **AD seems to be associated with a lower Mg status when compared to HCs**, while the scarcity of studies limited the findings about MCs.
https://pubmed.ncbi.nlm.nih.gov/35082658/ Association of Circulating Magnesium Levels in Patients With Alzheimer's Disease From 1991 to 2021: A Systematic Review and Meta-Analysis 2022
Alzheimer's disease (AD) remains a medical and social challenge worldwide. Magnesium (Mg) is one of the most frequently evaluated essential minerals with diverse biological functions in human body. However, the association between circulating Mg levels and AD remains controversial. We conducted a meta-analysis of 21 studies published between 1991 and 2021 to determine whether the Mg levels in the blood and cerebrospinal fluid (CSF) are abnormal in AD. **These results indicate that Mg deficiency may be a risk factor of AD and Mg supplementation may be a potentially valuable adjunctive treatment for AD.**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9029938/ Magnesium Orotate and the Microbiome–Gut–Brain Axis Modulation: New Approaches in Psychological Comorbidities of Gastrointestinal Functional Disorders 2022
Magnesium deficiency has been related to multiple somatic dysfunction, but neurologic, metabolic, osteo-muscular and cardiologic involvements have been the most studied until now. We propose a possible new theory that focuses on magnesium because its benefits have been recently suggested in both enteric and microbiome dysfunctions, but also in some psychiatric disorders [3,4,5]. We propose a narrative review that approaches the topic of magnesium, and especially magnesium orotate, **as a supportive key element of the gut–brain axis and an adjuvant of prebiotics, probiotics** and other therapeutic management in gastrointestinal diseases associated with psychological comorbidities, in both child and adult populations, as a possible future clinical approach.
https://pubmed.ncbi.nlm.nih.gov/25268773/ Magnesium protects cognitive functions and synaptic plasticity in streptozotocin-induced sporadic Alzheimer's model 2014
We also found that **magnesium sulfate reversed impairments in long-term potentiation** (LTP), dendritic abnormalities, and the impaired recruitment of synaptic proteins. Magnesium sulfate treatment also decreased tau hyperphosphorylation by increasing the inhibitory phosphorylation of GSK-3β at serine 9, thereby increasing the activity of Akt at Ser473 and PI3K at Tyr458/199, and improving insulin sensitivity. We conclude that **magnesium treatment protects cognitive function and synaptic plasticity by inhibiting GSK-3β in sporadic AD model rats,** which suggests a potential role for magnesium in AD therapy.

Manganese (both low and high levels are bad)

Sources: Shellfish, Nuts(hazelnuts,pecans), Brown rice, Oatmeal
RDA: 2.3mg/day for men, 1.8mg/day for women
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9372870/pdf/WJCC-10-7631.pdf Role of micronutrients in Alzheimer's disease: Review of available evidence 2022
Manganese is one of the essential micronutrients in the body. It is involved in oxidation-reduction, lipid synthesis and, protein degradation, which are mostly related to the alkylation of manganese. Various aromatic, heterocyclic aromatic, and aliphatic secondary amines, such as indole and resveratrol-derived amines, can be obtained by alkylation reaction[81]. **Most studies have found that AD can occur with decreased or normal levels of manganese[82**]. With rapid industrialization and the increasing environmental pollution, **excessive intake of heavy metal manganese will have a neurotoxic effect and promote neurodegeneration**. Astrocyte is the main stable cell type in the central nervous system. **Excessive intake of manganese can** affect the structure and function of astrocytes, as well as the synthesis and d**egradation of glutamate.** Effective **control of manganese neurotoxicity may be a potential strategy for preventing or slowing AD[83]**. Abnormal conformation of prion proteins in normal cells can lead to their transformation into pathogenic prion proteins, which can bind to manganese, copper, zinc, and other micronutrients, and thus induce AD[84]. Studies have shown the role of manganese in the diagnosis of AD. Manganese enhanced magnetic resonance imaging can be used to assess the level of pathological Tau accumulation[85]. **Treatment with Manganese chelating agents may play a role in neurodegenerative diseases such as AD**, providing a new strategy for the clinical treatment of AD[86]. AD is associated with a decline in learning and memory. **Use of naringin reduces amyloid accumulation, a manganese-induced form of AD in rats.**

It is suggested that naringin has a neuroprotective effect, which is closely related to the anti-oxidant, anti-inflammatory and anti-amyloid degeneration effect of naringin[87]. Manganese-rich nanocapsules were shown to improve cognitive ability in animal models with AD, which is related to the decrease of Tau protein in animal brain tissue[88].

https://pubmed.ncbi.nlm.nih.gov/28273828/ Association of Serum Manganese Levels with Alzheimer's Disease and Mild Cognitive Impairment: A Systematic Review and Meta-Analysis 2017

Manganese (Mn) is one of the most studied environmental heavy metals linked to Alzheimer's disease (AD). However, it remains unclear whether serum Mn levels are associated with AD and mild cognition impairment (MCI, a prodromal stage of AD). We conducted a metaanalysis to analyze the serum Mn levels in patients with AD and MCI. Random-effects meta-analysis showed that **patients with AD had significantly reduced serum Mn levels** compared with HC subjects (SMD = -0.39; 95% CI (-0.71, -0.08); p = 0.015). MCI individuals had a tendency toward reduced serum Mn levels compared with HC subjects (SMD = -0.31; 95% CI (-0.70, 0.08); p = 0.117). A significant decrease in serum Mn levels was found in patients with cognitive impairment (including both AD patients and MCI patients) (SMD = -0.37, 95% CI (-0.60; -0.13); p = 0.002). Finally, no significant differences were observed between AD and MCI patients in serum levels (SMD = 0.24; 95% CI (-0.23, 0.72); p = 0.310). **Our findings show that the serum Mn levels are lower in AD patients, and Mn deficiency may be a risk factor for AD.**

https://pubmed.ncbi.nlm.nih.gov/31546716/ New Insights on the Role of Manganese in Alzheimer's Disease and Parkinson's Disease 2019

Manganese (Mn) is an essential trace element that is naturally found in the environment and is necessary as a cofactor for many enzymes and is important in several physiological processes that support development, growth, and neuronal function. However, **overexposure to Mn may induce neurotoxicity and may contribute to the development of Alzheimer's disease (AD)** and Parkinson's disease (PD). The present review aims to provide new insights into the involvement of Mn in the etiology of AD and PD. Here, we discuss the critical role of Mn in the etiology of these disorders and provide a summary of the proposed mechanisms underlying Mn-induced neurodegeneration. In addition, we review some **new therapy options for AD and PD related to Mn overload.**

https://www.researchgate.net/publication/263432351_High_Manganese_A_Risk_for_Alzheimer's_Disease_High_Manganese_Induces_Amyloid-b_Related_Cognitive_Impairment

Excess manganese (Mn) in brain can be neurotoxic, implicated in several neurodegenerative disorders such as sporadic Alzheimer's disease (AD). However, little is known about the altered metal environment including elevated Mn in the progressive cognitive impairment of AD. Indeed, whether high Mn is associated with AD risk remains elusive. In the study, we recruited 40 Chinese elders with different cognitive statuses and investigated concentrations of Mn in whole blood and plasma amyloid-β (Aβ) peptides. Surprisingly, there were significant correlations of Mn with Mini-Mental State Examination score and Clinical Dementia Rating Scale score. In addition, plasma Aβ peptides increased with elevated Mn. Further studies both in vitro and in vivo demonstrated dose-related neurotoxicity and increase of Aβ by Mn treatment, which was probably caused by disrupted Aβ degradation. These data suggested that **high Mn may be involved in the progress of AD** as an essential pathogenic factor.

https://www.frontiersin.org/articles/10.3389/fnagi.2020.556008/full Manganese Exposure Aggravates β-Amyloid Pathology by Microglial Activation 2020

Mn exposure increased BACE1 expression and amyloidogenesis. We further determined that **Mn exposure promoted the activation of microglia both in 3×Tg-AD mouse brains and in cultured microglia cells, and increased the secretion of the inflammatory cytokines interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α)**. Taken together, these results suggest that Mn may increase the release of IL-1β and TNF-α from microglia that in turn stimulates the expression of BACE1 gene and protein and consequently Aβ production; this novel molecular mechanism not only advances our understanding about the amyloidogenic effect of chronic Mn exposure reported for special human populations but also indicates **Mn dyshomeostasis as a potential contributor to AD pathogenesis.**

https://selfhacked.com/blog/manganese/ Cognitive Function

Several enzymes important for brain function work only in the presence of manganese [13].

In a study of 296 school-age children, children with higher urine manganese levels had higher IQ. This relationship was especially pronounced in girls [14].

In another study of 404 school-age children, those with **very low or very high blood and hair levels of manganese had lower IQ scores**. Children in the middle of the scale, with roughly average blood and hair levels of manganese, had the highest IQ scores [15].

Finally, in a study of over 1,200 children, girls that had higher exposure to manganese before they were born performed better in cognitive tests. However, in the same study, high manganese exposure in early life adversely affected children's behavior. Once again, balanced manganese levels are important [16].

Both low and high manganese levels are linked to lower IQ in children. Balanced levels of manganese appear to be key.

https://pubmed.ncbi.nlm.nih.gov/31786641/ Changes of trace element status during aging: results of the EPIC-Potsdam cohort study 2020

Conclusions: In conclusion, in this population-based study of healthy elderly, decrease in Mn, Zn, and Se concentrations and increase in Fe, Cu, and I concentrations were observed over 20 years of follow-up. Further research is required to investigate dietary determinants and markers of TE status as well as the relationships between TE profiles and the risk of age-related diseases.

Mercury (not a micronutrient) (Selenium may help)also Cilantro?

https://pubmed.ncbi.nlm.nih.gov/33411216/ Mercury and Alzheimer's disease: a look at the links and evidence. 2021

This review demonstrates the involvement of mercury, in its different forms, in the **pathway of amyloid beta deposition and tau tangles formation**

https://pubmed.ncbi.nlm.nih.gov/30877448/ Insights into the Potential Role of Mercury in Alzheimer's Disease. 2019

Research reports on AD and relationships between Hg and AD indicate that neurotransmitters such as **serotonin, acetylcholine, dopamine, norepinephrine, and glutamate are dysregulated in patients with AD**. Many researchers have suggested that AD patients should be evaluated for Hg exposure and toxicity. Some authors suggest further exploration of the Hg concentrations in AD patients. Dysfunctional signaling pathways in AD and Hg exposure appear to be interlinked with some driving factors such as arachidonic acid, homocysteine, dehydroepiandrosterone (DHEA) sulfate, hydrogen peroxide, glucosamine glycans, glutathione, acetyl-L carnitine, melatonin, and HDL.

https://pubmed.ncbi.nlm.nih.gov/31861093/ A Hypothesis and Evidence That Mercury May be an Etiological Factor in Alzheimer's Disease. 2019

The abnormalities of minerals and vitamins, specifically aluminum, calcium, copper, iron, magnesium, selenium, zinc, and vitamins B1, B12, E, and C, that occur in patients with Alzheimer's disease, also occur in mercury toxicity. Aluminum has been found to increase mercury's toxicity. Likewise, **similar biochemical factors in AD are affected by mercury, including changes in blood levels of homocysteine, arachidonic acid, DHEA sulfate, glutathione, hydrogen peroxide, glycosamine glycans, acetyl-L carnitine, melatonin, and HDL**. Other factors seen in Alzheimer's disease, such as increased platelet activation, poor odor identification, hypertension, depression, increased incidences of herpes virus and chlamydia infections, also occur in mercury exposure

https://pubmed.ncbi.nlm.nih.gov/17628833/ Mercury and Alzheimer's disease] 2007

Latest therapeutic approaches to the treatment of Alzheimer disease **embrace pharmaceuticals which remove or bind metals from the brain**. Preliminary success has been documented with chelation of synergistic toxic metals (Fe, Al, Zn, Cu) and therefore also Hg.

https://pubmed.ncbi.nlm.nih.gov/36293098/ Dietary **Selenomethionine Reduce Mercury Tissue Levels** and Modulate Methylmercury Induced Proteomic and Transcriptomic Alterations in Hippocampi of Adolescent BALB/c Mice 2022

Methylmercury (MeHg) is a well-known environmental contaminant, particularly harmful to the developing brain. The main human dietary exposure to MeHg occurs through seafood consumption. However, seafood also contains several nutrients, including selenium, which has been shown to interact with MeHg and potentially ameliorate its toxicity. The aim of this study was to **investigate the combined effects of selenium (as selenomethionine; SeMet) and MeHg on mercury accumulation i**n tissues and the effects concomitant dietary exposure of these compounds exert on the hippocampal proteome and transcriptome in mice.

https://pubmed.ncbi.nlm.nih.gov/16898674/ Involvement of environmental mercury and lead in the etiology of neurodegenerative diseases. 2006

Taken together, a considerable body of evidence suggests that the **heavy metals lead and mercury contribute to the etiology of neurodegenerative diseases** and emphasizes the importance of taking preventive measures in this regard.

https://pubmed.ncbi.nlm.nih.gov/34831595/ Environmental Substances Associated with Alzheimer's Disease-A Scoping Review. 2021

For **mercury (Hg), association is possible but inconsistent. Regarding cadmium (Cd) and arsenic (As), the results are inconsistent but inclined towards possible associations** between the substances and the risk of disease. The evidence regarding lead (Pb) was weaker than for the other substances; however, possible associations exist

https://pubmed.ncbi.nlm.nih.gov/35216107/ Comprehensive Review Regarding Mercury Poisoning and Its Complex Involvement in Alzheimer's Disease 2022

Hg exposure was associated with numerous CNS disorders that frequently trigger Alzheimer's disease (AD). **Patients with AD have higher concentrations of Hg in blood and brain tissue**.

https://pubmed.ncbi.nlm.nih.gov/28929917/ Mercurius solubilis attenuates scopolamine-induced memory deficits and enhances the motor coordination in mice 2018

Results: In vitro studies have revealed merc sol 30 X to have maximum free radical and nitric oxide scavenging activity. Administration of merc sol 30 X to mice significantly reduced scopolamine induced memory deficits and motor incoordination in all the performance tasks. **The calcium ionophore, A23187 significantly altered the effect of merc sol in mice.** No major signs of toxicity were observed.

https://pubmed.ncbi.nlm.nih.gov/8914687/ Significant mercury deposits in internal organs following the removal of dental amalgam, & development of pre-cancer on the gingiva and the sides of the tongue and their represented organs as a result of inadvertent exposure to strong curing light (used to solidify synthetic dental filling material) & effective treatment: a clinical case report, along with organ representation areas for each tooth. However, these **mercury deposits, which commonly occur in such cases, were successfully eliminated by the oral intake of 100 mg tablet of Chinese parsley (Cilantro)** 4 times a day (for average weight adults) with a number of drug-uptake enhancement methods developed by the 1st author, including different stimulation methods on the accurate organ representation areas of the hands (which have been mapped using the Bi-Digital O-Ring Test), without injections of chelating agents.

Selenium **(enhance bio-availability of other, neuroinflammation, antioxidant, anti-inflamatory, metal chelator, gut Microbiota)**

Sources: Brazil Nuts(80ug/nut), Salman(40ug/serving), Pork/ham(48mcg), Macarone/enriched(37mcg), Turkey(31mcg), Brown rice(19mcg), Beef(18mcg), Egg(15mcg)

RDA: 55ug/day (Other says 75ug) max Recommend 400ug (~5Brazil Nuts)
https://ods.od.nih.gov/factsheets/selenium-healthprofessional/ Selenium: Fact Sheet for Consumers
Selenium, which is nutritionally essential for humans, is a constituent of more than two dozen selenoproteins that play critical roles in reproduction, thyroid hormone metabolism, DNA synthesis, and protection from oxidative damage and infection [1]. Selenium exists in two forms: inorganic (selenate and selenite) and organic (selenomethionine and selenocysteine) [2]. Both forms can be good dietary sources of selenium [3] Recommended Intake: 55 mcg/day The human body absorbs more than **90% of selenomethionine but only about 50% of selenium from selenite [6]**. daily supplementation with **120 mg ascorbic acid, 30 mg vitamin E, 6 mg beta-carotene, 100 mcg selenium, and 20 mg zinc for 8 years was associated with higher episodic memory and semantic fluency test scores 6 years after the study ended [59].**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9372870/pdf/WJCC-10-7631.pdf Role of micronutrients in Alzheimer's disease: Review of available evidence 2022
Selenium is one of the most common micronutrients in the body. It is involved in biological oxidation, cell differentiation, protein synthesis, and gene transcription. In particular, **selenium inhibits ACHE and butylcholinesterase, which has a positive effect on the treatment of AD[67]**. **Selenium is a central component of many antioxidant enzymes (glutathione peroxidase)** that regulate redox levels in the body and have a positive effect on the immune system[68]. **Selenium deficiency is believed to be involved in the causation of AD.** Selenium deficiency impairs immunity and leads to overproduction of oxidized products and amyloid-beta protein. Selenium can interact with metals by using selenomethionine and improve the body's antioxidant capacity'[69]. **Chondroitin sulfate selenium has been shown to improve spatial learning and memory impairment in mice with AD,** reduce the degree of synaptic edema of hippocampal neurons, and protect the integrity of mitochondria. The underlying mechanism involved activation of the P38 mitogen activated protein kinase signaling pathway by chondroitin sulfate selenium[70]. **Glutathione peroxidase 1 is a major antioxidant enzyme that has a protective effect against memory impairment induced by-amyloid in mice with AD**; this phenomenon is related to the activation of Erk signal pathway by glutathione peroxidase-1[71]. Memory impairment is the most well-known symptom of AD. The combination of nano-selenium (0.4 mg/kg) and stem cells increased the levels of brain- derived neurotrophic factor and reduced amyloid deposition in an Alzheimer mouse model; these results suggest that the combination of selenium and stem cells can reduce neurotoxicity in mice with AD[72]. Clinical studies have shown that AD is associated with cognitive decline. **Higher blood selenium levels in older people were shown to be associated with higher cognitive score**s; a general linear model was observed between blood selenium concentrations and cognitive function. It is **suggested that selenium ameliorates the decrease of cognitive ability**[73,74]. **Selenium is essential for brain health.** In a study of 984 men and 1032 women conducted between 2011 and 2014, selenium was found to be associated with cognitive function. The study involved assessment of whole blood selenium concentrations; there was no correlation between blood selenium concentration and sex. **The results indicated that adequate selenium was positively associated with cognitive ability in the elderly[**
https://pubmed.ncbi.nlm.nih.gov/35885402/ Evaluation of the Brewing Characteristics, Digestion Profiles, and Neuroprotective Effects of Two Typical Se-Enriched Green Teas 2022
As a functional beverage, **selenium (Se)-enriched green tea** (Se-GT) has gained increasing popularity for its superior properties in promoting health. In this study, we compared the brewing characteristics, in vitro digestion profiles, and **protective effects on neurotoxicity** induced through the amyloid-beta (Aβ) peptide of two typical Se-GTs (Enshi Yulu (ESYL) and Ziyang Maojian (ZYMJ), representing the typical low-Se green tea and high-Se green tea, respectively). ESYL and ZYMJ showed similar chemical component leaching properties with the different brewing methods, and the optimized brewing conditions were 5 min, 90 °C, 50 mL/g, and first brewing. The **antioxidant activities of the tea infusions** had the strongest positive correlation with the tea polyphenols among all of the leaching substances. The tea infusions of ESYL and ZYMJ showed similar digestive behaviors, and the tea polyphenols in the tea infusions were almost totally degraded or transferred after 150 min of dynamic digestion. Studies conducted in a cell model of Alzheimer's disease (AD) showed that the extract from the high-Se green tea was more effective for neuroprotection compared with the low-Se green tea. **Overall, our results revealed the best brewing conditions and digestion behaviors of Se-GT and the great potential of Se-GT or Se-enriched green extract (Se-GTE) to be used as promising AD-preventive beverages or food ingredients.**
https://pubmed.ncbi.nlm.nih.gov/31786641/ Changes of trace element status during aging: results of the EPIC-Potsdam cohort study 2020
Conclusions: In conclusion, in this population-based study of healthy elderly, decrease in Mn, Zn, and Se concentrations and increase in Fe, Cu, and I concentrations were observed over 20 years of follow-up. Further research is required to investigate dietary determinants and markers of TE status as well as the relationships between TE profiles and the risk of age-related diseases.
https://pubmed.ncbi.nlm.nih.gov/34569225/ Oral Administration of Resveratrol-Selenium-Peptide Nanocomposites Alleviates Alzheimer's Disease-like Pathogenesis by Inhibiting Aβ Aggregation and Regulating Gut Microbiota 2021
Alzheimer's disease (AD) is a neurodegenerative disease associated with amyloid-β (Aβ) deposition, leading to neurotoxicity (oxidative stress and neuroinflammation) and gut microbiota imbalance. **Resveratrol (Res) has neuroprotective properties, but its bioavailability *in vivo* is very low**. Herein, we developed a small **Res-selenium-peptide nanocomposite to enable the application of Res for eliminating Aβ aggregate-induced neurotoxicity and mitigating gut microbiota disorder in aluminum chloride ($AlCl_3$)** and d-galactose(d-gal)-induced AD model mice. Oral administration of TGN-Res@SeNPs improves cognitive disorder through (1) interacting with Aβ and decreasing Aβ aggregation, effectively **inhibiting Aβ deposition** in the hippocampus; (2) decreasing Aβ-induced reactive oxygen species (ROS) and **increasing activity of antioxidation enzymes** in PC12 cells and *in vivo*; (3) **down-regulating Aβ-induced neuroinflammation** via the nuclear factor kappa B/mitogen-activated protein kinase/Akt signal pathway in BV-2 cells and *in vivo*; and (4) **alleviating gut microbiota disorder**, particularly with respect to oxidative stress and **inflammatory-related bacteria such as *Alistipes*, *Helicobacter*, *Rikenella*, *Desulfovibrio,* and *Faecalibaculum*.** Thus, we anticipate that Res-selenium-peptide nanocomposites will offer a new potential strategy for the treatment of AD.
https://pubmed.ncbi.nlm.nih.gov/30295993/ A comparative study of resveratrol and resveratrol-functional selenium nanoparticles: Inhibiting amyloid β aggregation and reactive oxygen species formation properties 2018
Deposition of amyloid-β (Aβ) aggregates and formation of neurotoxic reactive oxygen species (ROS) are significant pathological signatures of Alzheimer's disease (AD). Resveratrol (Res) is an antioxidant with the potential to treat AD. However, the **bioavailability and solubility of Res is very low and it cannot entirely inhibit Cu^{2+} -induced Aβ42 aggregation at low concentration**. Herein, we **combine the unique Aβ absorption property of selenium nanoparticles with the natural antioxidant agent Res** to form Res@SeNPs. Our in vitro biological evaluation revealed that modification of Res with SeNPs provides a synergistic effect on Cu^{2+} -induced Aβ42 aggregation, ROS generation and, more importantly, protects PC12 cells from Aβ42-Cu^{2+} complexes-induced cell death. It is **believed that SeNPs can improve the application of Res in AD treatment as Res@SeNPs is more efficient than Res in reducing Aβ42 toxicity** in long-term use.
https://pubmed.ncbi.nlm.nih.gov/35982253/ Neuroprotective activity of selenium nanoparticles against the effect of amino acid enantiomers in Alzheimer's disease 2022
Alzheimer's disease (AD), the most prevalent neurodegenerative disease, is characterized by extracellular **accumulation of amyloid-beta protein (Aβ)**, which is believed to be the very starting event of AD neurodegeneration. In this work, D-Phe, D-Ala, and D-Glu amino acids, which are the non-occurring enantiomeric form in the human body, and also D-Asp and DL-SeMet, have proved to be amyloidogenic regarding $A\beta_{42}$ aggregation in TEM studies. These amyloidogenic amino acid enantiomers also **widened $A\beta_{42}$ fibrils up to 437%** regarding $A\beta_{42}$ alone, suggesting that $A\beta_{42}$ aggregation is enantiomerically dependent. To inhibit enantiomeric-induced amyloid aggregation, selenium nanoparticles stabilized with chitosan (Ch-SeNPs) were successfully synthesized and employed.
https://pubmed.ncbi.nlm.nih.gov/29481840/ Selenium, selenoprotein P, and Alzheimer's disease: is there a link? 2018
The essential trace element, selenium **(Se), is crucial to the brain** but it may be **potentially neurotoxic, depending on dosage** and speciation; Se has been discussed for decades in relation to Alzheimer's disease (AD). Selenoprotein P (SELENOP) is a secreted heparin-binding glycoprotein which serves as the main Se transport protein in mammals. In vivo studies showed that this protein might have additional functions such as a contribution to redox regulation. The current review focuses on recent research on the possible role of SELENOP in AD pathology, based on model and human studies. In relation to AD, various roles of SELENOP are discussed, i.e. as the **means of Se delivery to neurons, as an antioxidant, in cytoskeleton assembly, in interaction with redox-active metals (copper, iron, and mercury) and with misfolded proteins (amyloid-beta and hyperphosphorylated tau-protein).**
https://pubmed.ncbi.nlm.nih.gov/36293098/ Dietary Selenomethionine Reduce Mercury Tissue Levels and Modulate Methylmercury Induced Proteomic and Transcriptomic Alterations in Hippocampi of Adolescent BALB/c Mice 2022
Methylmercury (MeHg) is a well-known environmental contaminant, particularly harmful to the developing brain. The main human dietary exposure to MeHg occurs through seafood consumption. However, seafood also contains several nutrients, including selenium, which has been shown to interact with MeHg and potentially ameliorate its toxicity. The aim of this study was to investigate the combined effects of selenium (as selenomethionine; SeMet) and MeHg on mercury accumulation in tissues and the effects concomitant dietary exposure of these compounds exert on the hippocampal proteome and transcriptome in mice. The **dietary presence of SeMet reduced the amount of mercury in several organs, including the brain.**
https://pubmed.ncbi.nlm.nih.gov/35956381/ Effects of Selenium Supplementation in Patients with Mild Cognitive Impairment or Alzheimer's Disease: A Systematic Review and Meta-Analysis 2022
Elevated levels of oxidative stress could cause and aggravate Alzheimer's disease (AD). **Selenium (Se) is a trace element with antioxidant and anti-inflammatory activity with neuroprotective effects.** To evaluate the effects of Se supplementation in patients with AD or mild cognitive impairment (MCI) through a systematic review and meta-analysis, data were searched and collected from four electronic databases, including clinical trial studies published until December 2020, following the PRISMA guidelines. Studies that evaluated only **Se supplementation observed an improvement in Se levels, glutathione peroxidase (GPX) activity, and in some cognitive tests in MCI patients**; similarly, improvement in Se levels and mini-mental score was also observed in AD patients. Regarding supplementation of Se plus other nutrients, improvement in cognitive tests was observed in both AD and MCI patients. Therefore, **Se supplementation is a good alternative for patients with AD and MCI for improving Se levels and GPX activity.**
https://pubmed.ncbi.nlm.nih.gov/21593562/ Selenium and Alzheimer's disease: a systematic review 2011
Since considerable data have accrued showing that the essential trace element selenium (Se) might play different roles in the progression of AD, we conducted a systematic review of the literature regarding Se and AD. There is an absence of consistent clinical evidence as to whether supplementation of Se is beneficial in the treatment of AD and how Se levels are altered in brain, cerebrospinal fluid, and blood of patients with AD. Some longitudinal and cross-sectional studies, however, show an association of Se status and cognitive function. Findings from molecular biology reveal a decisive role of Se in the pathogenesis of AD. In summary, the current state of knowledge provides no evidence for a role of Se in the treatment of AD, but allows speculation on a potential preventive relevance.
https://pubmed.ncbi.nlm.nih.gov/1304229/ Selenium in the treatment of heavy metal poisoning and chemical carcinogenesis 1992
Selenium (Se) has been shown to counteract the toxicity of heavy metals such as cadmium, inorganic mercury, methylmercury, thallium and to a limited extent silver. Although not as effective as Se, **vitamin E significantly alters methylmercury toxicity** and is more effective than Se against silver toxicity. Vitamin E is very effective against lead toxicity but Se has little effect.

Silicon Silica (silicic acid)(decreases aluminum availability)

Sources: Green Beans(7mg), Bananas(4.8mg,13.6mg), Leafy Greens(4mg), Brown Rice(4.5mg), OatBran(3.3mg), Red Lentils(1.8mg), Raisins,Spinach,Seafood,OrganMeats,Sometimes Water
Max Daily: 700mg

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9372870/pdf/WJCC-10-7631.pdf Role of micronutrients in Alzheimer's disease: Review of available evidence 2022

Silicon is one of the most common micronutrients in the body It is divided into amorphous silicon and crystalline silicon, which exists in the form of silicate or silicon dioxide. Silicon is involved in collagen synthesis, immune system regulation, bone mineralization, and Tau phosphorylation[76]. **Silicon was shown to lower the risk of AD[77**]. Recent studies have shown the health benefits of silicon in humans. **Soluble silicic acid is a useful form of silicon in the human body**. The absorption, distribution, and metabolic characteristics of soluble silicic acid in human body are closely related to human health. The unique cross-linking ability of **soluble silicic acid and its antagonism to toxic aluminum may protect against AD[78].** Studies have shown an increase in the incidence of degenerative diseases in Western countries. Diet has a positive effect on AD. **Beer, which is rich in silicon and hops, plays an important role in preventing brain disorders.** This is primarily related to the ability of beer to regulate inflammation, oxidation, and cholinesterase activity[79]. Nerve growth factor (NGF) plays an important role in reducing the number of cholinergic neurons in AD. Studies have demonstrated the neuroprotective effect of NGF on rat pheochromocytoma PCL2 cells by using biodegradable porous silicon oxide carriers[80

https://pubmed.ncbi.nlm.nih.gov/31295866/ The Nutritional Components of Beer and Its Relationship with Neurodegeneration and Alzheimer's Disease 2019

Beer, as part of this protective diet, contains compounds such as **silicon and hops that could play a major role in preventing brain disorders**. Taking into account published results from our group and other studies, the **hypothesis linking aluminum intoxication with dementia and/or Alzheimer's disease** and the potential role of regular beer has also been considered. Beer, in spite of its alcohol content, may have some health benefits; nonetheless, its consumption is not adequate for all subjects. Thus, this review analyzed some promising results of non-alcoholic beer on several mechanisms engaged in neurodegeneration such as inflammation, oxidation, and cholinesterase activity, and their contribution to the behavioral modifications induced by aluminum intoxication. **Silicon and silicic acid may decrease aluminum bioavailability** by partially blocking its gastrointestinal tract uptake [152] and by impeding its reabsorption [153].

https://pubmed.ncbi.nlm.nih.gov/22976072/ There has been a plausible link between human exposure to aluminum and Alzheimer's disease for several decades 2013

Herein we are testing the hypothesis that **silicon-rich mineral waters can be used as non-invasive methods to reduce the body burden of aluminum in individuals with Alzheimer's disease** and a control group consisting of their carers and partners. We have shown that drinking up to **1 L of a silicon-rich mineral water each day for 12 weeks** facilitated the removal of aluminum via the urine in both patient and control groups without any concomitant affect upon the urinary excretion of the essential metals, iron and copper. We have provided preliminary evidence that over 12 weeks of silicon-rich mineral water therapy the body burden of **aluminum fell in individuals with Alzheimer's disease and, concomitantly, cognitive performance showed clinically relevant improvements in at least 3 out of 15 individuals**. This is a first step in a much needed rigorous test of the 'aluminum hypothesis of Alzheimer's disease' and a longer term study involving many more individuals is now warranted.

https://pubmed.ncbi.nlm.nih.gov/17435954/ The potential influence of silica present in drinking water on Alzheimer's disease and associated disorders 2007

Silica present in drinking water may be protective with respect to the decrease of cognitive function as it was suggested by several epidemiologic studies. Data from French cohort have demonstrated that aluminium in drinking water seems to have a deleterious effect and increased the risk of cognitive impairment when the silica concentrations were low. Moreover, it has been shown that the performances to a **cognitive test were positively correlated to the consumption of silica** and that the risk of Alzheimer's disease (AD) was reduced in subjects who had the higher daily silica intake compared to the others. The **silica is probably the natural antidote of the aluminium and could play a benefit role by decreasing the biodisponibility of aluminium, whose neurotoxicity is now clearly established.**

https://pubmed.ncbi.nlm.nih.gov/31035649/ Dietary Silicon and Its Impact on Plasma Silicon Levels in the Polish Population 2019

Silicon in nutritional amounts provides benefits for bone health and **cognitive function**.

https://pubmed.ncbi.nlm.nih.gov/2015936/ Silicon in foods and diets 1991

Silicon levels tend to be **higher in foods derived from plants** than in foods from animal sources. Foods highest in silicon include **grains, especially oats, barley** and some rice fractions. Average daily intakes of silicon probably range from about 20 to 50 mg/day with the lower values for animal-based diets and the higher values for plant-based diets.

https://pubmed.ncbi.nlm.nih.gov/19487017/ Dietary silicon intake in Belgium: Sources, availability from foods, and human serum levels 2009

Besides the dietary intake, serum silicon levels of various population groups support the **concept of essentiality of the element.** An in vitro dialysability of the element in a simulated digestion procedure is used as a surrogate of silicon uptake.Silicon was readily available from foods but this correlated inversely with the elemental content.**Serum silicon levels, as a function of age, gave indication of an important role of this element.**

https://pubmed.ncbi.nlm.nih.gov/33715532/ Silicon: A neglected micronutrient essential for bone health 2021

As for silicon dietary supplements, it has been shown that the combined treatment with **orthosilicic acid (6 mg), calcium, and vitamin D** has a potentially **beneficial effect on femoral BMD** compared to only use of calcium and vitamin D.

Vanadium **bis(maltolato)oxovanadium(IV) (BMOV)**

Sources: **Ground Parsley(1800ng/g)**, Dill seeds(431ng/g), **Black Pepper(985ng/g)**, Shellfish(100ng/g), Spinach(600ng/g), Mushrooms(50-20,000ng/g), Whole Grains+Cereals(5-30ng/g), Dairy(5-30ng/g),
RDA: none set, 10-30ug enough, 10-60mg might be safe

https://www.webmd.com/vitamins/ai/ingredientmono-749/vanadium Overview

Vanadium is a trace mineral regularly consumed in the diet. It's found in mushrooms, shellfish, black pepper, parsley, grains, and also drinking water.

https://www.researchgate.net/publication/
11367674_Influence_of_Chelation_and_Oxidation_State_on_Vanadium_Bioavailability_and_Their_Effects_on_Tissue_Concentrations_of_Zinc_Copper_and_Iron 2002

Today, **vanadium compounds are frequently included in nutritional supplements** and are also being developed for therapeutic use in diabetes mellitus. Previously, tissue uptake of vanadium from bis(maltolato)oxovanadium(IV) (BMOV) was shown to be increased compared to its uptake from vanadyl sulfate (VS). Our primary objective was to test the hypothesis that complexation increases vanadium uptake and that this effect is independent of oxidation state. A secondary **objective was to compare the effects of vanadium complexation and oxidation state on tissue iron, copper, and zinc.** Wistar rats were fed either ammonium metavanadate (AMV), VS, or BMOV (1.2 mM each in the drinking water). Tissue uptake of V following 12 wk of BMOV or AMV was higher than that from VS ($p < 0.05$). BMOV led to decreased tissue Zn and increased bone Fe content. The same three compounds were compared in a cellular model of absorption (Caco-2 cells). Vanadium uptake from VS was higher than that from BMOV or AMV at 10 min, but from BMOV (250 microM only, 60 min), uptake was far greater than from AMV or VS. These results show that neither complexation nor oxidation state alone are adequate predictors of relative absorption, tissue accumulation, or trace element interactions.

https://pubmed.ncbi.nlm.nih.gov/31970356/ Bis(ethylmaltolato)oxidovanadium(iv) inhibited the pathogenesis of Alzheimer's disease in triple transgenic model mice 2020

In this paper, 9-month-old triple transgenic AD model mice (3×Tg-AD) received bis(ethylmaltolato)oxidovanadium(iv) (BEOV) at doses of 0.2 mmol L^{-1} (68.4 μg mL^{-1}) and 1.0 mmol L^{-1} (342 μg mL^{-1}) for 3 months. **BEOV at both doses was found to improve contextual memory and spatial learning in AD mice**. It also improved glucose metabolism and protected neuronal synapses in the AD brain, as evidenced respectively by ^{18}F-labeled fluoro-deoxyglucose positron emission tomography (^{18}F-FDG-PET) scanning and by transmission electron microscopy. Our results suggested that BEOV reduced the pathological hallmarks of AD by targeting the pathways of PPARγ and PTP1B in 3×Tg AD mice.

https://pubmed.ncbi.nlm.nih.gov/35031965/ **An Adequate Supply of Bis(ethylmaltolato)oxidovanadium(IV) Remarkably Reversed the Pathological Hallmarks of Alzheimer's Disease in Triple-Transgenic Middle-Aged Mice 2022**

Bis(ethylmaltolato)oxidovanadium(IV) (BEOV), an organic bioactive vanadium compound with low toxicity and high bioavailability, has been studied as therapeutic agent against tuberculosis and diabetes. However, its neuroprotective effects have rarely been reported. Therefore, in this study, the potential application of BEOV in intervening AD cognitive dysfunction and neuropathology was evaluated. Both low- and high-dose of BEOV (0.2 mmol/L and 1.0 mmol/L) supplementation for 2 months improved the spatial learning and memory deficits of the triple-transgenic AD (3 × Tg AD) mice and mitigated the loss of synaptic proteins and synaptic dysfunction. By inhibiting the expression of amyloid-β precursor protein and β-secretase, and the phosphorylation of tau protein at Ser262, Ser396, Ser404, and Ser202/Thr205 residues, **BEOV reduced the amyloid-β deposition and neurofibrillary tangle formation in AD mouse brains and primarily cultured neurons**. Further analysis of the brain ionome revealed that **BEOV supplementation could significantly affect the concentrations of a variety of metals, most of which, including several AD risk metals, showed reduced levels, particularly with a high-dose intake**. Additionally, the elemental correlation network identified both conserved and specific elemental correlations, implying a highly complex and dynamic crosstalk between vanadium and other elements during long-term BEOV supplementation. Overall, our results suggest that **BEOV is effective in AD intervention via both ameliorating the disease related pathology and regulating metal homeostasis.**

https://pubmed.ncbi.nlm.nih.gov/34240269/ Bis(ethylmaltolato)oxidovanadium (IV) alleviates neuronal apoptosis through regulating peroxisome proliferator-activated receptor γ in a triple transgenic animal model of Alzheimer's disease 2021

Our results showed that **BEOV improved cognitive abilities and reduced the ER stress- and apoptosis-associated proteins in the brains of 3×Tg-AD mice**. In vitro administration of BEOV in primary hippocampal neurons and N2asw cells achieved similar results in repressing ER stress. In addition, cotreatment with GW9662 (an antagonist of PPARγ) effectively blocked these neuroprotective effects of BEOV, which provided strong evidence that PPARγ-dependent signaling plays a key role in protecting against ER stress and neuronal apoptosis in AD. In conclusion, our data demonstrated that BEOV alleviated neuronal apoptosis triggered by ER stress by regulating PPARγ in a 3×Tg-AD model.

Zinc

Sources: Red Meat(4.8mg), Shellfish, Legumes, Seeds, Nuts and Peanuts, Dairy, Eggs, Whole Grains, Dark chocolate
RDA: 8mg/day Women, 11mg/day Men (Max 40mg)
https://pubmed.ncbi.nlm.nih.gov/9164672/ Zinc and Alzheimer's disease: is there a direct link?
While **controversial, some studies indicate that total tissue zinc is markedly reduced in several brain regions of Alzheimer's patients.** At face value, it seems that a paradox exists between reports of a decrease in zinc in the Alzheimer's brain and the putative link to aberrant high zinc levels promoting plaque formation. An hypothesis to explain this inconsistency is presented.
https://pubmed.ncbi.nlm.nih.gov/21197404/ The role of zinc in Alzheimer's disease
Zinc binds to Aβ promoting its aggregation into neurotoxic species, and disruption of zinc homeostasis in the brain results in synaptic and memory deficits. Thus, zinc dyshomeostasis may have a critical role to play in the pathogenesis of AD, and the **chelation of zinc is a potential therapeutic approach**.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9372870/pdf/WJCC-10-7631.pdf Role of micronutrients in Alzheimer's disease: Review of available evidence 2022
Zinc is one of the essential micronutrients in the body and the second most abundant micronutrient in the central nervous system[28,29]. Zinc is involved in growth and development, wound healing, immune regulation, catalytic reactions, and substance synthesis. **Zinc also regulates excitatory and inhibitory neurotransmitters in brain tissue**[30,31]. As the **zinc content in the body decreases with age**, abnormal zinc metabolism may serve as a therapeutic target for AD. In particular, zinc and selenium or iron and zinc have been concomitantly used to treat AD[32,33].
Studies have shown that zinc release increases with age, especially in female rats, and that zinc deficiency leads to neuronal death; this phenomenon is related to the involvement of zinc in the recognition of neuronal receptors and ligands, which is one of the main risk factors for AD and its associated brain neuropathology[34]. On the contrary, **zinc supplementation was shown to improve cognitive deficit** and rescue the decline in key molecular targets of synaptic plasticity and insulin signaling in the hippocampus of rats with sporadic AD[35]. Oxidative stress plays a key role in neurode-generation and impaired cognitive function. **Diet rich in antioxidants is a novel strategy for prevention of AD**. Compared with healthy individuals, patients with AD showed significantly l**ower serum levels of Se, Cu, and Zn[36].** Studies have shown that the disorder of zinc dynamic equilibrium can cause abnormal synthesis and increased deposition of amyloid protein in brain tissue, and increase the degree of neuronal damage. The underlying mechanism involves binding of zinc to histidine residues of brain tissue-amyloid protein leading to the formation of amorphous aggregates of-amyloid protein, which then leads to the formation of age spots[37]. The **combination of zinc and copper was shown to accelerate the formation of amorphous aggregates of amyloid protein[38], and the high saturation magnetization of zinc ferrite was found to improve the formation of amorphous aggregates of amyloid protein[39]**. An increasing body of evidence has shown that the basal level of extracellular zinc in hippocampus is typically in the low nanomolar range, and that the increase in zinc content aggravates the neurotoxicity of amyloid protein[40]. Zinc was shown to increase the expression of amyloid precursor protein in a mouse model of AD, which in turn increased amyloid synthesis. Pathological dynamic equilibrium of copper, iron, and zinc promotes the deposition of amyloid proteins in brain tissue and affects structural changes in Tau Proteins. S100B is one of the most abundant proteins in the brain[41], which is involved in the regulation of amyloid deposition and zinc homeostasis. Use of zinc chelating agents can improve amyloid deposition levels by interfering with S100B[42]. Klotho protein is a zinc-rich protein which has neuroprotective, anti-inflammatory, anti- oxidant, and promyelination effects. Increasing serum Klotho protein can play a role in neuroprotection, anti-inflammation, and anti-oxidation[43]. Evidence suggests that **AD is associated with increased levels of Tau,** which is related to the presence of multiple zinc binding sites in the Tau protein. Low zinc levels stimulate Tau, leading to increased neurofibrillary tangle in the neurons[44]. The antioxidant zinc carboxylate inhibits the activity of acetylcholine esterase (ACHE) and butylcholinesterase and plays an anticholinesterase role, which indicates the benefit of zinc carboxylate in the treatment of AD[45]. Zinc homeostasis is involved in the pathogenesis of AD. **Zinc can significantly increase the activity of carnosine, which is beneficial in the treatment of AD[46].** Zinc deficiency can lead to a decrease in learning ability and memory in AD. Zinc supplementation (3mg/kg) was shown to improve learning and memory in a mouse model of AD, which may be related to the decrease in inflammatory activity in NLRP3[47]. Zinc can promote the aggregation of SFPQ in cultured neurons by regulating the nuclear SFPQ protein, which is an important marker of AD
https://pubmed.ncbi.nlm.nih.gov/35113349/ Associations Between Mild Cognitive Impairment and Whole Blood Zinc and Selenium in the Elderly Cohort. 2022
Some studies have shown that an imbalance in trace element homeostasis can lead to cognitive dysfunction, but data are lacking. The purpose of this study was to **investigate the association between whole blood zinc (Zn), selenium (Se), copper-zinc ratio (Cu/Zn), copper-selenium ratio (Cu/Se), and zinc-selenium ratio (Zn/Se) and mild cognitive impairment (MCI) in elderly Chinese** individuals. A total of 1006 participants with an average age of 71.70 years old were included in this study. Compared with healthy people, **MCI patients had higher whole blood Zn levels and lower Se levels,** and Cu/Zn, Cu/Se, and Zn/Se were also significantly different. Binary logistic regression analysis showed that Zn, Cu/Se, and Zn/Se exposure in the third tertile was associated with an increased risk of MCI, while Se exposure in the third tertile was associated with a reduced risk of MCI. After adjustment for sex, age, marital status, BMI, and living status, whole blood Zn, Se, Cu/Zn, Cu/Se, and Zn/Se were significantly associated with MCI risk, especially in elderly women.
https://pubmed.ncbi.nlm.nih.gov/31786641/ Changes of trace element status during aging: results of the EPIC-Potsdam cohort study 2020
Conclusions: In conclusion, in this population-based study of healthy elderly, decrease in Mn, Zn, and Se concentrations and increase in Fe, Cu, and I concentrations were observed over 20 years of follow-up. Further research is required to investigate dietary determinants and markers of TE status as well as the relationships between TE profiles and the risk of age-related diseases.