



# What role do metals play in Alzheimer's disease?

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## Abstract

Alzheimer's disease is the most common neurodegenerative disorder that usually occurs after the age of 65 for which there is currently no cure. The predominant feature of this disease is the appearance of beta amyloid plaques next to the neurons in the brain. Numerous studies have investigated the possible causes of the disease and in particular the role of metals. In the present study, while briefly reviewing the effect of various lifestyle factors on the incidence and prevalence of the disease, by presenting the latest clinical reports and cohort studies regarding the role of metals in the disease, we try to provide a comprehensive overview of this issue to the reader. Some studies have shown changes in the concentration of metals in the brain or body fluids of AD patients, while others have not indicated any change. Therefore, it can be concluded that metals are not causative factor, but they are risk factor in certain conditions.

**Keywords** Alzheimer · Metal ion · Aluminum · Copper · Lead · Mercury · Iron · Zinc · Manganese · Arsenic · Environmental factors

## Introduction

It is estimated that 1.5 billion people on Earth will be over 65 years of age by 2050. Aging is associated with changes in different cellular processes caused by different factors that lead to reduce function of various organs and tissues, including the brain. Old age is also a major risk factor for neurodegenerative diseases, including Alzheimer's disease (AD) [1]. AD is a deadly disease that is characterized by beta-amyloid (A $\beta$ ) plaques and neurofibrillary tangles outside and inside brain neurons, respectively [2] (Fig. 1). Unfortunately, this disease can be detected in the advanced stages and after the onset of symptoms, which is too late for any effective treatment, and on the other hand, the drugs approved for its treatment do not have a significant effect on the well-being of patients [3]. For these reasons, there is an urgent need to identify and treat this devastating disorder.

AD is a complex and multifactorial disease, and various factors such as amyloid protein, tau protein, metals, and other issues have been studied as its possible causes [4]. Naturally, there are small amounts of metals such as zinc, copper, and iron in our body that are essential for the proper functioning of the brain and body and involved in various processes such as energy production, oxygen transport, and the production and regulation of many important molecules in the body [5]. Apart from essential metals, there are other metals that people are exposed to or contaminated with in various ways [6]. The body is resistant to small amounts of these elements (e.g., aluminum and lead) [7–10]; however, if these elements are not excreted due to the intake of large amounts of them or kidney failure, they can be deposited in the body and can cause adverse effects in the brain and cause neurological complications [7]. Relatively much research has been done on the relationship between different metals and AD, but there is no consensus. In this review article, while briefly reviewing the preventable factors, the role of metals in the development of this disease has been specifically addressed.

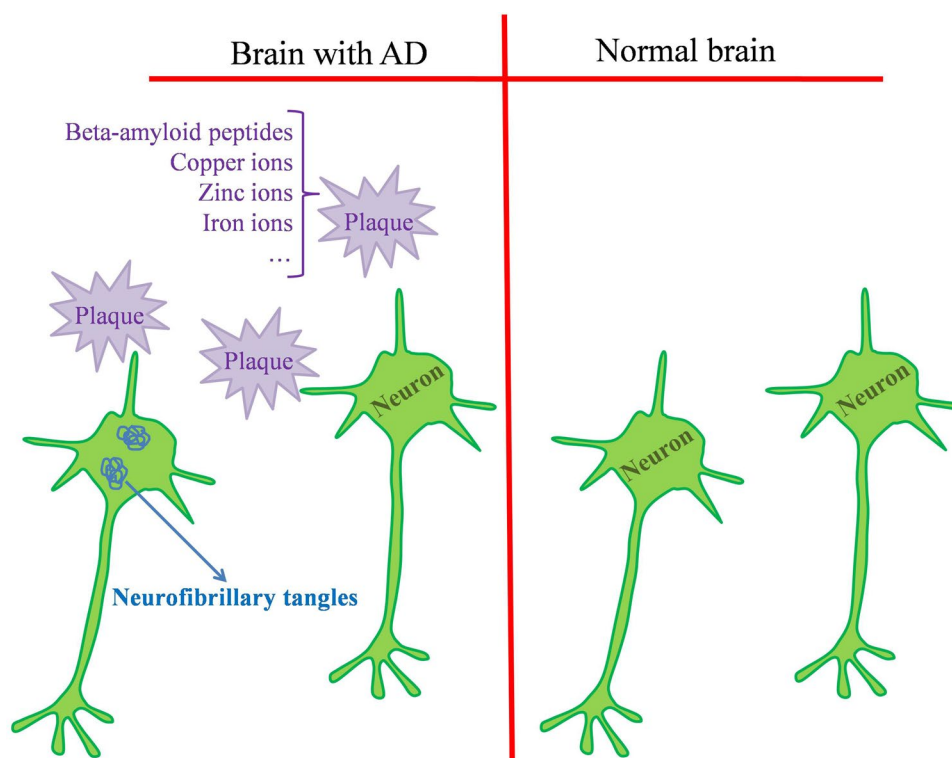
In the past, diagnostic efforts have focused on patients who are in the dementia stage, but more recently, the importance of the long pre-dementia period (a period in which clinical symptoms have not yet developed) has been noted. The initial stage, which is silent and asymptomatic, is called

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**Fig.1** Significant signs of Alzheimer's disease in the brain



the pre-clinical stage and is characterized by symptoms that begin approximately 20 years before the onset of the disease [11].

Unfortunately, the reason of AD has not yet been diagnosed and therefore there is no cure for it. However, epidemiological studies have provided information on its risk factors that, in addition to helping to identify the cause, can provide appropriate measures to prevent it [12]. According to these documents, in addition to factors such as aging, gender and the presence of genetic mutations that cannot be avoided, preventable risk factors including "environmental factors" and "lifestyle" are also involved in causing this deadly disease [13].

### Preventable influencing factors in Alzheimer's disease

So far, no drug has been shown to be effective in treating AD; therefore, studies in this area have focused on healthy people who may be at risk for AD to prevent AD with this strategy. Since genetics is not often the cause, other factors have come to the fore, and the impact of "environmental factors" and "lifestyle" on the progression of AD is becoming increasingly apparent [14]. Diabetes mellitus, smoking, depression, mental inactivity, physical inactivity, and poor diet were initially identified as risk factors [15], which later added blood pressure, obesity, and low education to this list

[16]. It is worth noting that diet is a highly modifiable lifestyle factor that can reduce the risk of AD [17].

Risk factors for cardiovascular diseases such as unhealthy diets, physical inactivity, and stress (anxiety) are now also known as risk factors for AD [12, 18]. Interestingly, a significant association has recently been reported between the risk factors for cardiovascular disease in the "mid-life" and amyloid deposition in the "later years" [19].

Smoking in a large fraction of sufferers' population has made it a serious risk factor. Tobacco smoke contains hundreds of chemicals that are toxic to neurons and can damage neurons by causing oxidative stress and inflammation [16, 20]. Among the compounds in cigarette smoke, it has been shown that Pb(IV) can interact with the N-terminal of A $\beta$  and cause it to precipitate [21].

Although some cohort studies have shown that the risk of developing AD has been halved in people who have had high physical activity [22, 23], no randomized controlled trial (RCT) study has confirmed this [24]. However, in a recent study [25], the researchers did not find any neuroprotective effects of physical activity and suggested that reduced physical activity may be due to dementia.

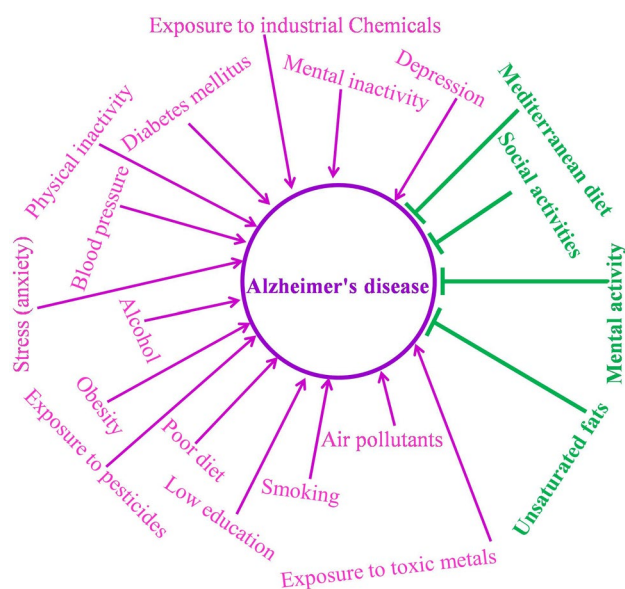
Cohort and interventional studies have shown that taking vitamin supplements cannot prevent AD, but high fat, diabetes, and lifestyle factors (alcohol, smoking, obesity, etc.) increase the risk of AD on average, and fish, the Mediterranean diet, unsaturated fats, and social activities play a protective role [26]. In addition, epidemiological studies

and animal model researches have shown a positive effect of caffeine consumption on the brain function and prevention of AD [27–29]. Some reports have suggested that these effects are due to improve antioxidant status, reduce lipid peroxidation, and inhibit acetylcholinesterase, adenosine deaminase, and arginase activities in the brain and cortex [30, 31]. Acetylcholinesterase [32], adenosine deaminase [29, 33, 34], and arginase [35] are enzymes that inhibition of them can be considered as a possible solution in the field of disease control or treatment.

Environmental factors include exposure to toxic metals, pesticides, industrial chemicals, and air pollutants. Exposure to these environmental pollutants and their biological accumulation during a person's lifetime can cause inflammation and neurological disease leading to the development of AD [36]. Since the 1980s, much attention has been paid to the role of metals in AD because various cell processes, such as energy production, repair, and proliferation, depend on metals. On the other hand, a significant part of the population is usually exposed to metals such as aluminum, lead, iron, and copper, which are obtained from various sources and are all considered risk factors [37] (Fig. 2).

## The role of metals in the development of Alzheimer's disease

One of the main cellular processes that is impaired with age is the homeostasis of metals and the function of proteins related to them, which directly and indirectly affect the disorders of aging [1]. Metals are natural compounds that



**Fig. 2** Protective (green) and risk (pink) factors of Alzheimer's disease

easily lose electrons and are converted to cations. Metals are found throughout the earth, including the atmosphere, the earth's crust, and water, and therefore can accumulate in plant and animal organisms. Among the 35 natural metals, 23 have a density of more than  $5 \text{ g/cm}^3$  and an atomic weight of over 40, which are called heavy metals [38]. This group of metals is not only famous for their high density, but also because of their detrimental effects on ecosystem and living organisms [39].

Metals are generally classified to essential and non-essential groups [40]. An essential metal must have several properties: first, it must be present in human tissues, second, its absence in the body can cause severe and irreversible damage to biological functions, and third, the reduction in physiological function returns to normal with appropriate supplements [5]. Some metals, such as copper, cobalt, iron, nickel, magnesium, molybdenum, chromium, selenium, manganese, and zinc, have functional roles and are essential for a variety of biochemical and physiological activities in the body [41]. Although large amounts of some of these metals can be harmful to the body, very small amounts of non-essential metals such as cadmium, mercury, lead, chromium, silver, and arsenic have delusional effects and can cause acute or chronic intoxication [39].

## Metals associated with Alzheimer's disease

### Aluminum

The only metal previously was considered as a risk factor for AD was aluminum that is controversial today [37]. Aluminum is the third most common element in the nature after oxygen and silicon; however, no role has been identified for it in living systems. Aluminum is broadly used in medicine, pharmacy, food industry, and cosmetics, also, in the manufacture of kitchen utensils and food preparation, and through these ways, it enters the human body [42]. Aluminum is a light metal, and its alloys with other metals are strong and durable; therefore, it is used in the manufacture of kitchen utensils. Numerous studies have shown that aluminum leaks into food from aluminum containers and foils, but leaking depends on many factors such as degree of acidity, temperature, cooking method, food content, cooking time (contact with aluminum), and the presence of fluoride, sugar, salt, and organic acids [43].

On the other hand, the absorption of aluminum is affected by elements such as iron, calcium, zinc, and citrate [44]. Aluminum foil is widely used for food packaging, cosmetics, and chemicals. Aluminum foil is easy to use, disposable, having twice the heat transfer of other metals; therefore, it is widely used for cooking. Aluminum leakage has been observed in some foods due to cooking in aluminum foil.

Although the amount of food aluminum in this method has been reported to increase up to 40 times, this amount of aluminum is not a concern for healthy people [44]. Antacids are other notable cases in the field of aluminum intake. Antacids are aluminum-rich drugs that are widely used. Regular use of antacids has not been linked to AD in either case–control or cohort studies [45].

In 1965, researchers injected very high doses of aluminum (accidentally) into rabbits, increasing tau protein deposition and increasing plaque in the brain led to speculation that aluminum in cans, cookware and processed foods, and even drinking water can cause dementia [46]. However, subsequent studies have shown that food contact with aluminum containers cannot increase the concentration of aluminum in the blood so much that it reaches the millimolar levels, the levels needed to reduce glucose metabolism in the brain. In fact, the pathophysiological mechanisms of "non-diet" lead to the accumulation of aluminum, while most dietary aluminum is excreted by the kidneys [47]. On average, about 10 mg of aluminum enters the human body daily, of which about 9.6 mg is obtained from food and the rest is due to the use of aluminum containers. It is noteworthy that in healthy people, about 0.01–1% of the received aluminum is absorbed into the blood and the rest is excreted from the body [42, 43]. In addition, the Food and Agriculture Organization and the World Health Organization have reported in 2011 that receiving 2 mg/kg body weight per week is safe [43].

Tea is one of the few plants that has a high accumulation of aluminum in its leaves [48], but the prevalence of dementia in areas with high consumption of tea has not been reported. On the other hand, epidemiological and systematic studies have shown that the green tea has positive effects in preventing dementia and AD, and drinking tea is considered as a natural remedy [49–51]. In fact, the amounts of various metals, including aluminum, that enter the body through tea drinking are not high enough to raise concerns about AD [52]. In addition, some studies have shown that the tea extract in *C. elegans* worm model of AD delays some of the complications of the disease and increases the life of the worm [53].

Some studies in 2013 found that the long-term effects of aluminum dust inhalation by miners, which were common between 1950 and 1960 (even up to the time of the study), did not make a significant difference in the development of AD [54]. In addition, a meta-analysis study in 2015 found that occupational exposure to aluminum was not significantly associated with AD [55]. In general, several studies on the relationship between aluminum in drinking water and AD have reported different results [56]. Some believe that aluminum in drinking water is involved in causing disease [57] and some consider it ineffective [58–60] and even protective [61]. A meta-analysis study in 2016 with a total of 10,567 participants [62] has shown that people who were

chronically exposed to aluminum were 71% more likely to develop AD. Moreover, a recent study has shown that aluminum concentration is very high in the brains of familial AD patients [63]. The presence of aluminum in the core of amyloid plaques has already been reported [64]. In addition, it has been shown that aluminum accumulates selectively in the arterial walls from the aorta to the PCA (posterior cerebral artery; the main artery in the hippocampus) so that it precipitates 9 times as much as the aortic wall in the PCA wall [65].

## Copper

The copper needed by the body is provided by the water and food consumption. The average copper concentration in the US tap water is about 0.02–0.075 mg/L, and drinking water makes up about 6–13% of the copper intake [66]. On the other hand, the National Research Council (USA) has declared that the intake of 1.3 mg/L copper in drinking water or in the milk of infants receiving copper-enriched milk is safe. In addition, the European Chemicals Agency has reported environmental copper concentrations without concern [67]. Foods containing copper include the organs meats (brain, tongue, liver, offal, etc.), nuts, seafood, seeds, legumes, and whole grains [68]. The average daily intake of copper in the USA is 1–1.6 mg/day for adults [67].

Copper can be as monovalent or divalent cation in food, but only is in divalent form in water. The initial uptake of copper occurs actively in the form of monovalent in the gastrointestinal tract [69]. Divalent copper is rapidly reduced on the surface of intestinal cells by metallo-reductase activity [70]. Exposure to too much copper internalizes the copper transporter in the intestine, and as a result, copper absorption decreases and its excretion increases [71]. In fact, daily copper intake in the range of 0.57–6.9 mg has been shown to have no effect on plasma copper concentrations [72]. Some evidence indicated that AD patients who received copper for 1 year did not show any unpleasant changes compared with those who received placebo. Therefore, the causative effect of "excess copper" to develop the disease is ruled out [73]. Excessive copper intake seems to be problematic when accompanied with saturated fats. A prospective epidemiologic study on 3,718 participants showed that the rate of cognitive decline was tripled in those who had high saturated fat diets with high copper intake over a 6-year period, that is, their global cognitive score (the mean of the 4 tests) decreased as much as 19 years over 6 years [74].

Some studies have suggested that copper in food is healthy, but inorganic copper, which is in vitamin supplements and tap water, can pass through the liver and enter the bloodstream and brain directly. It is especially dangerous when accompanied by saturated and trans fats [75, 76]. Copper binds to the histidine or proteins such as albumin and

macroglobulin in the bloodstream [71, 77]. Some reports have found no clear correlation between copper uptake and factors such as zinc, ascorbic acid, and fiber, but some have reported an inverse relationship between copper, zinc, and iron uptake [68].

Involvement of copper transporter genes in Menkes and Wilson's diseases where copper deficiency and accumulation occur, respectively, also neurological disorders and cognitive decline that occur in both of them, can indicate the effect of impaired copper homeostasis on serious damages to nerve cells [78]. A $\beta$  homeostasis in the brain of AD mouse models was impaired by reducing copper intake [79]. Another study showed that reducing copper intake in healthy men led to a significant reduction in the plasma opioid peptides that returned to normal levels with copper intake [80, 81]. Opioid peptides have analgesic and wound-healing properties. A longitudinal cohort study has revealed that anxiety and pain are major problems for dementia patients [82]. On the other hand, various studies have shown an association between opioid system dysfunction and AD (reviewed in [83]).

## Iron

Iron accumulation in the brain occurs naturally with age. Data from a research project on healthy people revealed that in addition to aging, smoking and body mass index also have a significant effect on iron accumulation in the brain and its distribution similar to AD [84]. Too much iron can be toxic [85]. On the other hand, iron deficiency causes anemia, which increases the risk of dementia [86]. Some data have shown that the women with the highest cognitive scores had the lowest levels of copper and iron in their blood [87]. Also, another research has indicated that people with high hemoglobin (an indicator of iron content) are more likely to develop AD [88], while the latest meta-analysis shows that serum iron is lower in AD patients compared to controls [89]. In addition, recent findings suggest that iron concentrations in deep gray matter and neocortical areas are higher in AD patients, and changes in iron levels in the temporal lobe over time are associated with cognitive decline in AD patients [90]. A similar study shows that increased cortical iron in AD patients is closely related to the rate of cognitive decline, presumably by stimulating oxidative stress, inflammation, or ferroptosis cell death [91]. The results of new researches indicate that low-oxidation-state iron, which is dangerous in AD and increases the oxidative stress, can be caused by the interaction of A $\beta$  with ferritin (inert iron) [92].

## Zinc

Zinc plays essential roles in various functions related to AD such as A $\beta$  production and tau phosphorylation; thus, zinc dyshomeostasis can disrupt these functions of zinc

and interfere with the development or progression of AD [93]. Some studies have shown that zinc deficiency, a metal that involves in DNA synthesis and short-term learning and memory, may lead to cognitive problems [94, 95], and several small studies have shown that taking zinc supplements can help to improve brain function [96–98]. The latest meta-analysis shows that AD patients have less serum zinc than their healthy counterparts do [89]. New findings show that mRNA or protein levels of major zinc transporters have changed at different stages of AD in brains of patients [99]. Although both copper and zinc accumulate in amyloid plaques, the evidence generally suggests a protective role for zinc. It has been shown that zinc can decrease the toxicity of amyloid peptides by changing their conformation in plaques [100].

## Lead

Lead is a heavy metal with which acute poisoning is common and severe poisoning with this element leads to known neurological symptoms [101]. However, mild lead poisoning is associated with symptoms of AD [102, 103]. There is also evidence that lead poisoning in early life can lead to increased DNA methylation, amyloid production, and APP expression in old age [104–106]. Lead is a chronic and potent toxin in the brain that has detrimental effects through a variety of mechanisms, including mitochondrial dysfunction, dysfunction of neurotransmitters, and inappropriate nerve responses (by substituting calcium and zinc) [107]. Recently, data from an animal study have revealed that lead in sub-toxic and toxic levels straightly attacks cerebral vascular system and damages the blood–brain barrier (BBB) [108]. Furthermore, another study shows that in subchronic exposure to lead, lead accumulates in choroid plexus and decreases the clearance of A $\beta$  from the cerebrospinal fluid (CSF), which in turn results in an increase in A $\beta$  in the CSF [109]. Although special attention is paid to the toxicity of lead during development, due to the ability of lead to cross the BBB, its toxicity in adults is also very important. About 95% of lead accumulation occurs in bone [110], where it can replace calcium and be stored in hydroxyapatite (the main bone and tooth material). While the half-life of lead in the blood is about 30 days, its half-life in bone is about 20–30 years, and various factors cause it to be released from the bone marrow into the bloodstream [107]. It is noteworthy that the latest meta-analysis has shown that the blood lead concentration in AD patients has decreased [111].

## Mercury

Mercury is another heavy metal with which acute poisoning is common and leads to well-known neurological symptoms [101] and the mild poisoning caused by it causes



AD symptoms [102, 103]. Mercury has a half-life of about 20 years in the brain, and its effects in AD are exacerbated due to the brain being specifically targeted by mercury [112]. Recent studies show that mercury binds specifically to A $\beta$  and prevents it from fibrillization [113, 114]. The results of a meta-analysis show that AD patients have more blood mercury than healthy people [111]. Moreover, a recent cross-sectional study has reported a significant relationship between increased exposure to ethylmercury and cognitive decline [115].

Mercury is a highly toxic pollutant for living systems. In general, dental amalgams are the first source of mercury accumulated in the human brain [116]. The results of some studies show that a high prevalence of memory impairment among dentists and dental staff (who are more exposed to mercury than others) has been reported [117, 118]. Moreover, personnel are more likely than others to complain of problems such as neurobehavioral problems, decreased psychomotor speed, decreased cognitive flexibility, attention deficit, and also memory loss, fatigue, and sleep problems [117, 119]. An investigation in 2019 that was conducted on more than 16,666 dementia patients and 33,332 healthy controls showed no relationship between amalgam use and the spread of dementia but indicated that those who had dementia showed more accelerated progression of the disease depending on the amount of amalgam used [120]. However, public health agencies, including the FDA, the US Public Health Service, and the World Health Organization, have approved the use of amalgam as a safe, durable, and cost-effective material for dental restorations [120].

Air pollution with this metal (mercury leakage from mines) and its accumulation in seafood has increased its toxicity potential for humans. On the other hand, preservatives containing mercury in vaccines are still controversial. Mercury in vapor and in organic compounds can enter hydrophobic tissues. Many studies have shown a causal link between exposure to mercury and the incidence and progression of AD, and this is not surprising because mercury is a powerful inhibitor of many biochemical pathways, each of which can damage the central nervous system and reduce cognitive function. The association of this metal with AD needs further study [116, 121].

## Manganese

Manganese is an essential metal; therefore, its toxicity to neurons occurs in large quantities, and long-term environmental exposure to low levels of it has been shown to cause serious damage to the brain cells [122]. Particular attention is paid to this metal in Parkinson-like syndrome, which is very common in occupational exposure [123]. The proposed mechanism of neurotoxicity for this metal is not specific to Parkinson's disease and may play a role in other neurological

diseases such as AD [110, 124]. A cohort study on more than 1,000 people in Australia showed that manganese was lower in the serum of AD patients than in healthy people [110]. A more recent meta-analysis, including 836 cases and 1,254 healthy controls, also found that serum manganese levels in AD patients were significantly decreased compared with controls [125]. These results contradict some studies on smaller groups that have shown an increase in plasma manganese concentration in AD patients [126, 127]. It is noteworthy that manganese is distributed differently in different parts of the blood, with about 66% in red blood cells, 30% in buffy coat, and 4% in plasma [128].

Some data indicate that plasma A $\beta$  increases with increasing manganese and there is a significant relationship between manganese and Mini-Mental State Exam (MMSE) and Clinical Dementia Rating Scale scores of the elderly subjects with different cognitive statuses [129]. Further investigation in this study, both *in vitro* and *in vivo*, suggest that manganese may cause neurotoxicity by disrupting A $\beta$  degradation. Recent studies have confirmed this issue because they have shown that treatment of SH-SY5Y cells with manganese reduces APP expression [130, 131]. Numerous other studies have shown that manganese can play a role in the neurotoxicity of AD by causing oxidative stress, mitochondrial dysfunction, and malfunction of neurotransmitter systems (reviewed in [132]).

## Magnesium

Some studies have suggested that plasma magnesium is lower in AD patients than that in healthy people [133] and other studies have shown a link between serum magnesium concentrations and the degree of AD [134]. Moreover, other findings have revealed that magnesium is lower in some brain areas in AD patients compared to controls [135, 136]. The results of a systematic review have indicated that magnesium in CSF and hair of AD patients are less than those of controls, but there is no difference in their serum magnesium [137]. A randomized trial in 2015 has shown that cognitive function in older participants remarkably improved by magnesium supplementation [138]. However, a prospective population-based cohort study with a total of 9,569 participants has indicated that both low serum magnesium and high serum magnesium are correlated with an increased risk of dementia [139].

Furthermore, recent studies provide evidence that magnesium supplementation can reduce methylation of the APOE gene (an important risk factor for AD) in people over 65 years of age and significantly improve their cognitive function as well [140]. On the other hand, previous evidence has shown that increased APOE methylation is correlated with age-associated cognitive decline [141]. Moreover, it has been shown that magnesium-induced neurotoxicity is

determined by protein phosphatase 2 A (PP2A) demethylation, which is correlated with tau hyperphosphorylation and shortage of spatial learning and memory in rat models, and possibly S-adenosylmethionine (SAM) deficiency in the hippocampus determines the loss of PP2A methylation [142]. PP2A is a main tau phosphatase, which its activity is performed by the methylation state of catalytic C subunit, and SAM—downstream metabolite of methionine—acts as a methyl donor in transmethylation pathways [142]. In addition, some studies show that magnesium deficiency can result in detrimental effects in endothelium integrity and disrupt endothelial barrier functions [143] and other experimental evidence shows that magnesium can decrease permeability of *in vitro* BBB model and increase clearance of A $\beta$  through BBB [143].

### Cobalt

Cobalt is an essential component of cobalamin (vitamin B12) and is necessary for the normal functioning of the nervous system, the production of DNA, and energy metabolism [112]. MMSE has revealed that serum cobalt content can be directly related to cognition [144]. Moreover, vitamin B12 deficiency has been shown to ultimately increase the risk of AD and leads to disease progression in patients [145, 146], and also, some studies have shown the decrease in cobalt in the serum of AD patients [147]. In addition, recent *in vitro* studies have shown that vitamin B12 binds directly to tau protein and prevents its fibrillization [148] and other data show that cobalt complexes prevent tau aggregation [149]. Cobalt complexes also affect beta deposition and stabilize non-toxic species of beta deposits [150]. Cobalt-Schiff base complexes have been suggested as potential therapeutic agents for various situations including as inhibiting protein aggregation [151].

### Arsenic

Arsenic causes toxicity in human, and its two main sources are drinking water and food [152, 153]. It has been revealed that serum arsenic levels are inversely related to cognitive test scores [154], and its high levels can cause phosphorylation of tau protein (a protein that is highly phosphorylated and precipitated in AD) [155] and transcription of APP [156]. An *in vitro* study showed that arsenic in APP overexpressing cells increased APP expression but decreased A $\beta$  production [157]. Although it has been hypothesized that arsenic may be the cause of AD [158], no significant difference has been observed between serum arsenic in AD patients and healthy cases [154]. However, a recent study has reported a positive correlation between soil arsenic concentration and AD mortality [159] and other studies have reported a negative correlation between groundwater

arsenic levels and neuropsychological performance [160, 161]. In addition, other findings have shown that high fat diet (in mice) exacerbates arsenic-induced memory impairment three times [162]. The permeability of the BBB to this metal has made it a powerful neurotoxin. By inducing pro-inflammatory cytokines such as TNF- $\alpha$ , IL-6, it directly affects the cortex, cerebellum, and especially microglia [163]. Pro-apoptotic signaling and activation of caspase by arsenic cause large-scale tissue damage [163].

MMSE scores from a case–control study showed that high urinary inorganic arsenic or low dimethylarsinic acid has significant associations with AD risk [164]. The molecular mechanisms of arsenic neurodegeneration effects involved mitochondrial dysfunction, oxidative stress, epigenetics, changes in neurotransmitter homeostasis and synaptic transmission, inflammation, and cell death pathways (reviewed in [165]).

### Cadmium

Cadmium is a food contaminant that can be tolerated up to 62  $\mu\text{g}/\text{kg}$  of body weight daily [166]. Cigarette smoke is another source of cadmium contamination [167]. People on normal diets get about 40–60% of this amount from the diet, but eating oysters, crustaceans, and spinach can increase that amount. However, some studies believe that this tolerable range should be reduced [166]. A meta-analysis study revealed that cadmium in the blood of AD patients was significantly higher compared to controls [111]. Findings from a study on 2,068 participants aged  $\geq 60$  years old [168] have indicated that elevated blood cadmium is accompanied with poorer cognitive function. Moreover, another study on a total of 4,064 participants aged  $\geq 60$  years old in the USA showed a significant relationship between blood cadmium levels and AD mortality in the elderly [169]. Animal studies have shown that cadmium can bypass the BBB [170] and even can alter the tight junction integrity of the BBB [171]. Some data from an *in vitro* study show that cadmium intervenes in the regulation of genes related to calcium regulation and other genes associated with microtubules dynamics and neuroprotection [172].

### Sodium

The association between high sodium intake and hypertension and cardiovascular disease has led to a general recommendation to reduce sodium intake to improve cardiovascular health [173]. A systematic review study shows that although different associations have been reported between sodium levels and cognition, the only clinical trial study has shown that lower sodium intake is associated with improved cognition. In addition, three of the four high-quality studies have shown that higher sodium intake is associated with

**Table 1** Possible mechanisms of metals involvement in Alzheimer's disease

Metals	Possible mechanisms of metals involvement in Alzheimer's disease
Aluminum	Tau protein deposition [46], amyloid plaque formation [46], selective accumulation in the arterial walls from the aorta to the PCA [65]
Copper	A $\beta$ homeostasis [79], reduction of the plasma opioid [80, 81]
Iron	Stimulating oxidative stress, inflammation, ferroptosis cell death [91]
Zinc	A $\beta$ production, tau phosphorylation [93]
Lead	Mitochondrial dysfunction, dysfunction of neurotransmitters, inappropriate nerve responses [107], damage of the BBB [108]
Mercury	Preventing A $\beta$ fibrillization [102, 103]
Manganese	Disrupting A $\beta$ degradation [130, 131], oxidative stress, mitochondrial dysfunction, malfunction of neurotransmitter systems [132]
Magnesium	Reducing methylation of the APOE gene [140], demethylation of protein phosphatase 2A [142], decrease permeability of in vitro BBB model [143]
Cobalt	Prevention from tau fibrillization [148], prevention from tau aggregation [149], stabilization of non-toxic species of A $\beta$ deposits [150]
Arsenic	Phosphorylation of tau protein [155], transcription of APP [156], reducing A $\beta$ production [157], inducing pro-inflammatory cytokines production [163], pro-apoptotic signaling and activation of caspase [163], mitochondrial dysfunction, oxidative stress, epigenetics, changes in neurotransmitter homeostasis and synaptic transmission, inflammation, involvement in cell death [165]
Cadmium	Alteration the integrity of the BBB [171], regulation of genes related to calcium regulation and other genes associated with microtubules dynamics and neuroprotection [172]
Sodium	A $\beta$ uptake from brain into capillary endothelial cells [176], tau hyperphosphorylation [177]

cognitive impairment [174]. Another study showed a direct link between nail sodium levels and the clinical stages of AD [175]. Some evidence suggests that sodium-coupled oligopeptide transport system is involved in A $\beta$  uptake from brain into capillary endothelial cells and this transfer occurs in the direction of the sodium concentration gradient [176]. Furthermore, it has been shown that a salt-rich diet in mice resulted in cognitive dysfunction associated with tau hyperphosphorylation [177].

### Other metals

There is a report on an increase in molybdenum in the blood of AD patients [178]. Moreover, it has been reported that potassium and rubidium are significantly reduced in all intracellular components in the AD brain. However, no significant change in their concentrations in serum, erythrocytes, and CSF was observed in patients and in the disease stages, which shows that, contrary to the hypothesis of impaired BBB in AD patients, ion leakage from the blood is minimal [179].

### Conclusion

Metals play important roles in the human body including maintaining cell structure, regulating gene expression, neurotransmission, and antioxidant responses. However, the accumulation of high levels of them in the nervous system can be toxic, cause oxidative stress, impair mitochondrial function, and alter the activity of many enzymes.

Metals accumulation can lead to permanent damages such as neurological diseases [40].

It is noteworthy that a significant fraction of population is exposed to high level of metals that are toxic to the nervous system. In addition, it has been observed that genetics and other trace metals can have a synergistic effect with them and increase their toxicity, in which case it is necessary to reconsider their use, whether in food (fish) or medicine (used in vaccines and other drugs) [180].

In general, various studies have shown the dyshomeostasis of some essential metals and the presence of some non-essential metals in AD patients, but a systematic study in 2017 shows that there is no evidence that metals are causative in AD [181].

Overall, the diversity of information about the relationship between metals and AD (Table 1) clarifies two points. First, because the change in metals concentrations with AD is not significant in some studies, metals cannot be considered as the cause of the disease. Second, due to the significant change in metal concentrations with AD in another part of the studies, it can be concluded that in favorable conditions for the disease, changes in metal homeostasis or the presence of toxic metals can contribute to the occurrence and progression of the disease.

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## Compliance with ethical standards

**Conflict of interest** It is declared that we do not have any conflicts of interest regarding the present study.

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