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Review article

Metals linked with the most prevalent primary neurodegenerative dementias in the elderly: A narrative review

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ABSTRACT

The ageing population has been steadily increasing worldwide, leading to a higher risk of cognitive decline and dementia. Environmental toxicants, particularly metals, have been identified as modifiable risk factors for cognitive impairment. Continuous exposure to metals occurs mainly through dietary sources, with older adults being particularly vulnerable. However, imbalances in the gut microbiota, known as dysbiosis, have also been associated with dementia. A literature review was conducted to explore the potential role of metals in the development of cognitive decline and the most prevalent primary neurodegenerative dementias, as well as their interaction with the gut microbiota. High levels of iron (Fe) and copper (Cu) are associated with mild cognitive impairment (MCI) and Alzheimer's disease (AD), while low selenium (Se) levels are linked to poor cognitive status. Parkinson's disease dementia (PDD) is associated with elevated levels of iron (Fe), manganese (Mn), and zinc (Zn), but the role of copper (Cu) remains unclear. The relationship between metals and Lewy body dementia (LBD) requires further investigation. High aluminium (Al) exposure is associated with frontotemporal dementia (FTD), and elevated selenium (Se) levels may be linked to its onset. Challenges in comparing studies arise from the heterogeneity of metal analysis matrices and analytical techniques, as well as the limitations of small study cohorts. More research is needed to understand the influence of metals on cognition through the gut microbiota (GMB) and its potential relevance in the development of these diseases.

1. Introduction

For decades, the ageing population has been growing steadily around the world. According to World Health Organization, 1 out of 6 people worldwide will be over 60 years old by 2030 (WHO, 2020). Ageing is a natural process that refers to the set of physical and physiological changes produced in an organism over time (WHO, 2015). It is characterised by a progressive decline in physical and mental capacities, increasing the risk of disease and eventually leading to death (WHO, 2015). Among the diseases associated with ageing, cognitive impairment which affects different domains, such as memory, learning, or day-to-day decision-making, stands out.

Cognitive impairment, along with age, are major risk factors for dementia, especially in men (Petersen et al., 2010). In fact, about 15% of cases of mild cognitive impairment (MCI) annually progress to Alzheimer's disease (AD) or other dementias, such as frontotemporal dementia (FTD) or Lewy bodies dementia, which includes Lewy bodies dementia (LBD) and Parkinson's disease dementia (PDD) (Petersen et al., 2014). Hence, the identification and reduction of modifiable risk factors of cognitive impairment is essential for healthy ageing (Cabrera et al., 2021). In this regard, the scientific community has been highlighting the importance of environmental toxicants as one of these risk factors for years (Belaidi and Bush, 2016; Huat et al., 2019; Squitti et al., 2019).

Metals include highly toxic metals and metalloids that are characterised by high molar mass and high toxic capacity, even at low concentrations (Budi et al., 2022). Highly toxic metals are widely distributed in the environment and are commonly used both in numerous areas (such as agriculture, mining, technological and medical applications) and at home. There is also occupational exposure, which

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occurs mainly in workers in the aforementioned areas. Some metals, like iron (Fe), copper (Cu), zinc (Zn), or calcium (Ca) are known as essential elements because of their involvement in various biological processes. Iron is an essential element for the proper development of brain functions, as it is involved in cellular processes such as neurotransmitter synthesis, myelination of neurons, and mitochondrial function (Gong et al., 2021). Copper is important in Fe metabolism and the proper maintenance of bones and nervous system. It is mostly bound to ceruloplasmin, its main transporter from the liver to the rest of the body, although a small fraction can circulate freely (Rozzini et al., 2018). Zinc has a major role in the development of the immune system and other biological functions such as antioxidant mechanisms and DNA repair (Socha et al., 2021). Calcium is involved in several processes, such as cell growth, neuronal development, and cellular homeostasis (Sukumaran et al., 2021). Others, such as selenium (Se), magnesium (Mg), or manganese (Mn) are considered trace elements. Selenium plays a major role in the body's antioxidant mechanisms. It can be found in both inorganic (selenate) and organic (in various selenoproteins) forms (Nascimento et al., 2021). Magnesium plays a critical role in brain function and mood since it is essential for optimal nerve transmission and it is involved in the formation of membrane phospholipids (Botturi et al., 2020). Also, Mn participates as a cofactor in different enzymes responsible for the detoxification of reactive oxygen species (ROS) (Kornblith et al., 2018). Finally, elements such as arsenic (As), cadmium (Cd), lead (Pb), mercury (Hg), or aluminium (Al) are called toxic elements because of their toxic potential and already demonstrated link with different diseases (Yadav et al., 2021; Yang et al., 2018). Arsenic can cause learning and memory disorders and mood deficits (Jakubowski et al., 2021). Concerning Cd, it can be transported directly through the blood-brain barrier (BBB) and eventually accumulates in the brain activating signaling pathways involved in inflammation, oxidative stress, and neuronal apoptosis (Liu H. et al., 2021). On the other hand, the effects of Pb include memory loss, reduced neural signaling and decreased learning ability (Fathabadi et al., 2018). Mercury has been reported to induce cognitive impairment in the brain (Yadav et al., 2021). In addition, Hg has multiple toxic effects which include the generation of ROS and autoimmune inflammation (Pamphlett and Bishop, 2022). Aluminium has not been associated with any known biological function, but its capacity to induce inflammatory, autoimmune, and neurotoxic responses has been reported (Dey and Singh, 2022). Additionally, it can cause damage to the integrity of the intestinal barrier, leading to alterations in the composition of the gut microbiota (Hao et al., 2022).

Due to the wide distribution of metals in the environment, the exposure to these toxicants is continuous and occurs via different routes, being dietary the most relevant, followed by dermal and inhalation routes. Therefore, since elderly are one of the most vulnerable groups (Sanchini et al., 2022), it is necessary to determine the effects of metals in this population group.

Moreover, imbalances in the gut microbiota (GMB) occur during the ageing process (DeJong et al., 2020; Haran et al., 2019). In addition to age, other factors that can alter the gut microbiota include diet, antibiotic use, exercise, smoking, and host genetics (Gomaa, 2020). Furthermore, differences in gut microbiota have been described in various geographical regions (Saji et al., 2019; Vogt et al., 2017). These imbalances, known as dysbiosis, can influence the central nervous system (CNS) through the gut-brain axis. This bidirectional communication channel between brain and peripheral organs enables the GMB to modulate both regions and has been linked to different types of dementia (Benakis et al., 2020). The GMB can secrete metabolites such as short-chain fatty acids (SCFA), which have been associated with anti-inflammatory properties. Low abundances of SCFA-producing bacteria have been reported in patients with MCI, AD, and Parkinson's disease (PD), which is consistent with the inflammatory processes observed in these diseases (Haran et al., 2019; Li W et al., 2017; Wu et al., 2021). Furthermore, differences in the abundance of certain bacterial taxa associated with different forms of dementia have been described, suggesting the possibility that each dementia may present a specific microbiota pattern (Barichella et al., 2019; Unger et al., 2016; Zhuang et al., 2018).

Although the gut microbiota is attracting the attention of the scientific community and is being investigated, we consider reviewing their possible interaction with metals in the development of the onsets aforementioned.

The present literature review was aimed at exploring the potential role of metals in the development of AD, LBD and FTD, with MCI as an early stage of cognitive decline in humans. In addition, an attempt was made to detect whether the concentrations of these toxicants were related to the gut microbiota.

2. Methods

PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Scopus (https://www.scopus.com) were used as databases to retrieve studies from scientific literature. The search covered studies published within the last 5 years to obtain an up-to-date exploration of the latest advancements in the field.

We used a combination of the following keywords: "humans" or "patients" or "subject" or "participants" or "person" or "population" or "individuals" or "volunteers" and "elderly" or "aged" and "heavy metals" or "trace elements" and "dementia" or "cognitive impairment" or "mild cognitive impairment" or "Alzheimer's Disease dementia" or "Lewy Bodies dementia" or "Parkinson's Disease dementia" or "Frontotemporal dementia". A total of 325 articles were retrieved from the literature.

Next, we conducted a second search to find possible interactions between metals and microbiota related to cognitive decline with a combination of the following keywords: "humans" or "patients" or "subject" or "participants" or "person" or "population" or "individuals" or "volunteers" and "elderly" or "aged" and "heavy metals" or "trace elements" and "microbiota" or "gastrointestinal microbiome" or "gut brain axis". A total of 40 articles were retrieved from the literature.

Among them, only original and peer-reviewed articles in English or Spanish, with an elderly (more than 60 years old) human population, were selected. A total of 242 articles were retrieved from the literature. After that, reviews, systematic reviews, and duplicates between the two databases were discarded. Out of the 196 accessed articles for eligibility, 136 were excluded for not being related to dementia, not containing metal analysis, or including younger populations. Finally, 60 articles were selected to further review. Fig. 1 illustrates the search strategy.

3. Results and discussion

3.1. Alzheimer's disease (AD) and mild cognitive impairment (MCI)

The most studied highly toxic metals and trace elements in relation to AD and MCI were Cu (12 articles), Fe (11 articles), Se (13 articles), and Zn (7 articles). They are followed by Cd (6 articles), Pb (4 articles), As (4 articles), and Al (4 articles). References to Ca (3 articles), Hg (3 articles), and Mg (2 articles) were less abundant. Tables 1 and 2 shows the articles included in this review.

3.1.1. Copper

Rozzini et al. (2018) and Shere et al. (2018) discuss whether Cu contributes to the development of AD because of its role in generation of β-amyloid and the phosphorylation of Tau protein, which favours inflammatory processes and an increase of ROS concentrations.

Several studies have reported a positive association between serum Cu levels and cognitive impairment. Zhang et al. (2022) described concentrations of Cu associated with poor cognitive performance in older adults aged 60 and above (OR = 1.519, 95% CI: 1.050–2.197, P = 0.026). Li et al. (2019b) found that elevated plasma Cu levels correlated with poor scores on the Digit Symbol Substitution Test (working

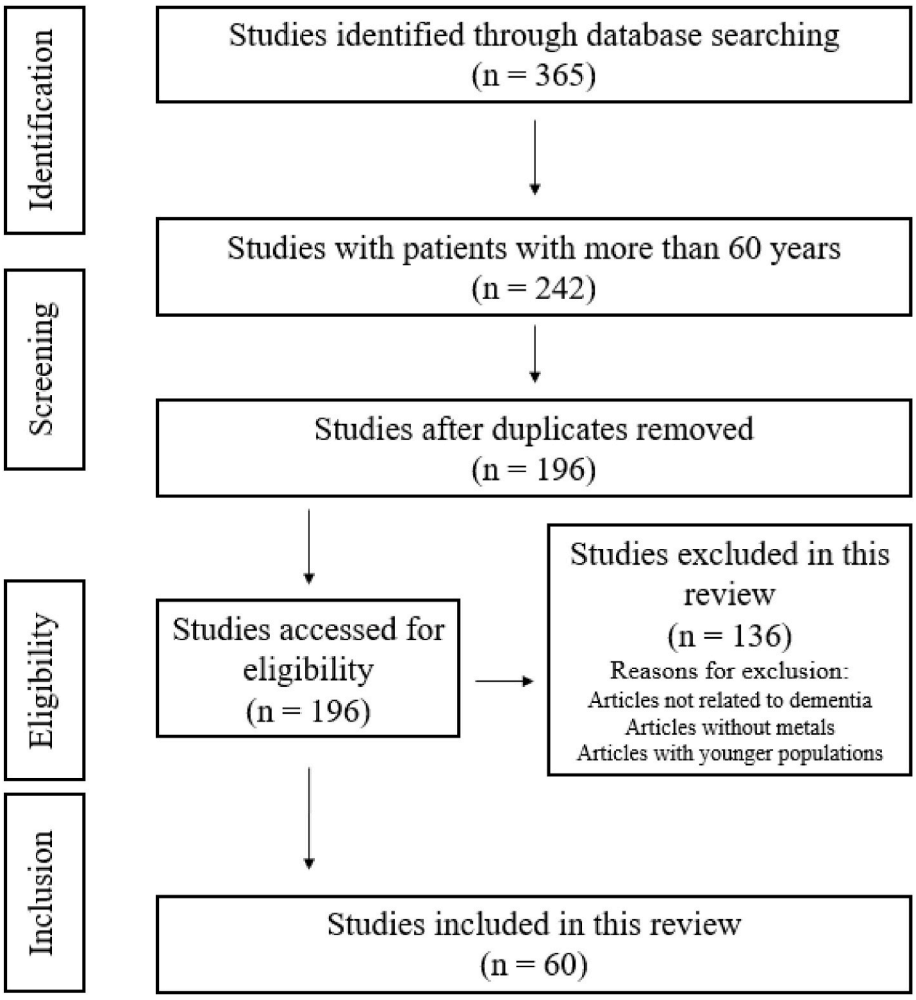

Fig. 1. Flow chart of the search strategy.

memory, processing speed, and attention) when evaluating 2503 American participants aged 60 years old or more. In turn, Socha et al. (2021) described higher Cu/Zn ratios in serum of 110 AD patients. Interestingly, in patients with Cu concentration above the average, a negative correlation with the results of the Mini-Mental State Examination Test (MMSE) was found. The MMSE is a cognitive screening test in which lower scores are associated with greater cognitive impairment. Moreover, the higher the Cu concentration, the greater the cognitive impairment (Gu et al., 2022; Jakubowski et al., 2021; Vaz et al., 2018). In accordance with those results, Giacconi et al. (2019) performed a clinical trial in 95 AD patients treated with acetylcholinesterase inhibitors, which showed cognition improvements and a reduction in plasmatic Cu concentration. Also, a decrease in the Cu/Zn ratio resulted in a reduction of inflammatory processes.

On the other hand, Rozzini et al. (2018) developed a new method to measure free Cu in serum of AD and MCI patients, finding elevated levels of Cu (36.3 ± 21.7 μg/L and 30.2 ± 15.2 μg/L vs 19.1 ± 7.3 μg/L), but without any correlation with MMSE results. In turn, some studies have reported low plasma Cu levels positively associated with AD (Ashraf et al., 2019; Shere et al., 2018). However, these studies have some limitations, like a very modest number of samples compared to Li et al. (2019b).

Furthermore, increased levels of Cu in serum have also been linked to hereditary AD cases. In turn, high Cu levels in serum were found in elderly patients carrying the e4 allele of APOE (Leko et al., 2021). Yadav et al. (2021) reported increased serum levels of Cu in AD patients, along with the overexpression of APP, PSEN1, PSEN2 and APOE4 genes. Nevertheless, they were unable to establish a correlation between Cu concentration and gene expression, may due to the limited size of the sample they employed.

3.1.2. Iron

Increased levels of Fe have been associated with oxidative stress processes and cognitive impairment (Jakubowski et al., 2021; Yumoto et al., 2018). Therefore, several studies have attempted to elucidate the potential role of Fe in the aetiology of AD, with heterogeneous results. Jouini et al. (2021) described a high Fe concentration (1.525 ± 0.779 μmol/100 mL vs 0.797 ± 0.238 μmol/100 mL, $P < 0.001$) in cerebrospinal fluid (CSF) of AD patients. Additionally, they observed a decrease in the concentration of the ceruloplasmin-transferrin complex (Cp-Tf), as well as total Fe, in the plasma of patients (Ashraf et al., 2019; Gong et al., 2021). In fact, the Cp-Tf complex participates in the regulation of Fe levels and is one of the main antioxidant systems in the body. Its dysregulation can lead to oxidative stress damage and cognitive deficits. Other oxidative stress markers, such as 8-hydroxy deoxy deoxyguanosine which is present in the nucleus of nerve cells, have been reported to colocalise highly with elevated Fe concentrations in CSF from AD patients (Yumoto et al., 2018). The simultaneous presence of Fe and these markers would hinder nuclear DNA repair processes, leading to nerve cell degradation.

In turn, Vaz et al. (2018) found significant elevated levels of Fe (13 mg/L vs 10 mg/L, $P < 0.001$) in blood of 32 AD patients, correlating positively with advanced cognitive stages of the disease. Controversially, in a more recent study it has been reported a decreased Fe

Table 1
Summary of Alzheimer's Disease studies with their most relevant goals.

Number of samples	Metals studied	Matrix	Country	Results	Reference
32	Al, As, Cd, Hg, Pb, Se	Self-administered questionnaire	Italy	No correlation between metals studied and cognitive measures was found in AD patients.	Adani et al. (2020)
44	Ca, Cu, Fe, P, Se, Zn	Plasma	United Kingdom	↓ Fe and ↑ Zn are associated with AD patients.	Ashraf et al. (2019)
40	Se	CSF Serum	Australia	Selenium levels weren't differed between healthy controls and AD patients.	Cardoso et al. (2019)
27	Pb	Serum	Iran	↑ Pb was associated with AD.	Fathabadi et al. (2018)
95	Cu, Zn	Plasma	Italy	↓ Cu and ↓ Zn in plasma of AD patients weren't associated with changes in MMSE.	Giacconi et al. (2019)
3131	Fe	Serum	United States	↓ Fe in AD patients.	Gong et al. (2021)
106	Ca, Fe, Mg	CSF Serum	Tunis	↓ Ca in CSF of AD patients. ↓ Fe in serum and ↑ Fe in CSF of AD patients.	Jouini et al. (2021)
12	Fe	Brain	The Netherlands	Iron caused neurodegeneration of microglia by modifying their cellular phenotype.	Kenkhuis et al. (2021)
40	As, Se	Hair Nail	Turkey	↑ As and ↑ Se were found in hair and nails of AD patients.	Koseoglu et al. (2021)
52	B, Ca, Co, Cr, Cu, Fe, Mg, Mo, Mn, Na, Zn	CSF Plasma	Croatia	↑ Ca, Cu and Mg in carriers of APOE4.	Leko et al. (2021)
22	Fe	Brain imageing	China	Iron deposition in the basal ganglia and reduction in blood perfusion in multiple regions was observed during the progression of MCI to AD.	Li D. et al. (2020)
2068	Cd	Whole blood	United States	↑ Cd was associated with worse cognitive function.	Li H. et al. (2018)
2332	Cu, Fe, Se, Zn	Self-administered questionnaire	United States	↓ Cu, ↓ Se and ↓ Zn were associated with cognitive impairment.	Li et al. (2019b)
1867	Cd	Whole blood	China	↑ Cd was associated with worse scores on various cognitive tests.	Liu H. et al. (2021)
34	Se	Plasma	Brazil	↓ Se were found in AD patients.	Nascimento et al. (2021)
32	Fe	Brain imageing	Republic of Korea	↑ Fe in motor cortex of patients with AD.	Park et al. (2019)
36	Cu	Serum	Italy	↑ Cu in MCI compared to healthy controls. No correlation between Cu and cognitive measures was found.	Rozzini et al. (2018)
44	Cu	Serum	India	↓ Cu were positively associated with AD.	Shere et al. (2018)
110	Cu, Se, Zn	Serum	Poland	↓ Se and ↓ Zn were found in AD patients.	Socha et al. (2021)
236	Fe	CSF	United States	↑ Fe were associated with Tau protein levels in AD patients.	Spotorno et al. (2020)
79	Se	Serum	Iran	Se co-supplementation for 12 weeks to patients with AD improved cognitive function and some metabolic profiles.	Tamtaji et al. (2019)
9	Fe	Brain	Austria	↑ Fe were found in temporal gyrus of AD patients.	van der Weerd et al. (2020)
34	Cu, Fe, Se	Plasma	Brazil	↑ Cu and ↑ Fe were found in AD patients. Selenium levels showed no difference between healthy controls and AD patients.	Vaz et al. (2018)
50	Al, As, Cd, Cu, Fe, Hg, Pb, Zn	Serum Whole blood	India	↑ Al, ↑ Cd, ↑ Cu and ↑ Hg were found in AD patients. ↓ Fe and ↓ Zn were found in AD patients.	Yadav et al. (2021)
82	As, Cd, Hg, Pb, Se	Urine Plasma	Taiwan	↑ urine As were associated with an increased risk of AD. ↓ plasma Se were found with AD patients.	Yang et al. (2018)
NA	Al, Fe	Human cells	Japan	Colocalization of Al and Fe in the nucleus of nerve cells might induce oxidative damage.	Yumoto et al. (2018)

AD: Alzheimer's Disease, CSF: cerebrospinal fluid, MMSE: Mini-Mental State Examination, MCI: Mild Cognitive Impairment, NA: Not available.

concentration in serum in patients with MCI and brain atrophy. However, these authors also reported that Fe concentration in CSF colocalised with β-amyloid plaques and negatively affected several cognitive domains, such as semantic memory, verbal episodic memory, and attention and processing speed. The relationship between Fe and β-amyloid was also reported by Kenkhuis et al. (2021) in a study of histological sections of AD patients' brains. This study demonstrated that a subset of iron-accumulating activated microglia exhibited dystrophic morphologies and was the predominant microglia detected in amyloid plaques.

In addition to β-amyloid, Fe has been linked to other hallmarks of AD. Using a methodology based on quantitative susceptibility mapping (QSM), a positive association was found between Fe concentration in CSF and Tau protein levels in 236 AD patients (Spotorno et al., 2020). Moreover, Fe is increased in the brain areas of higher blood perfusions in AD and MCI patients (Li D. et al., 2020). This is consistent with observed disruptions in the BBB, which would facilitate Fe accumulation. Interestingly, a study of 79 healthy elderly people also found elevated Fe concentrations in the basal ganglia, being negatively correlated with verbal memory and executive functions (Biel et al., 2021). In turn, elevated levels of Fe were positively associated with increased demyelination of nerve cells, which is related to the loss of the cognitive abilities.

Finally, some authors have focused on exploring the relationship between Fe and AD-related gene expression. For example, Yadav et al. (2021) evaluated 50 Indian AD patients and no correlations were found between low serum Fe levels and gene overexpression of APP, PSEN1, PSEN2, and APOE4. In turn, Leko et al. (2021) compared CSF Fe levels and APOE4 expression in 126 Croatian AD patients and 52 MCI patients and reported similar findings. Hence, according to these studies, Fe does not have a direct action on AD-related gene expression patterns.

3.1.3. Selenium

Several studies have tried to determine Se effects on the aetiology of AD, with heterogeneous results. Mostly, low Se concentrations, compared to the average of the individuals studied, have been associated with an increased risk of cognitive impairment (Yan et al., 2020). In a study of 34 Brazilian AD patients, lower plasma Se and erythrocyte Se

Table 2
Summary of Mild Cognitive Impairment studies with their most relevant goals.

Number of samples	Metals studied	Matrix	Country	Results	Reference
79	Al, Cu, Fe, Hg, Mn, Pb, Zn	Hair Soil	Portugal	↑ Mercury levels in hair in dementia patients.	Pinto et al., 2019
40	Se	CSF Serum	Australia	Selenium levels weren't differed between healthy controls and MCI patients.	Cardoso et al. (2019)
215	Cu	Whole blood	China	↑ Cu in the elderly was related to the occurrence of MCI, especially in men.	Gu et al. (2022)
467	Cd	Whole blood	United States	↑ Cd were associated with low cognitive performance.	Huang and Ren, 2022
266	Al, As, Cu, Fe, Si	Serum	United States	↑ seric Al were negatively associated with attention/ processing speed and executive function. ↑ seric Cu were associated with verbal episodic memory. ↑ seric Fe were negatively associated with semantic memory, verbal episodic memory and attention/ processing speed.	Jakubowski et al. (2021)
52	B, Ca, Co, Cr, Cu, Fe, Mg, Mo, Mn, Na, Zn	CSF Plasma	Croatia	↑ Ca, Cu and Mg in carriers of APOE4.	Leko et al. (2021)
22	Fe	Brain imageing	China	Iron deposition in the basal ganglia and ↓ blood perfusion in multiple regions observed during the progression of MCI to AD.	Li D. et al. (2020)
95	Fe	Brain imageing	Republic of Korea	↑ Fe in motor cortex of patients with MCI.	Park et al. (2019)
375	Cd	Urine	China	↑ urinary Cd were associated with increased risk of cognitive impairment.	Peng et al. (2020)
36	Cu	Serum	Italy	↑ Cu in MCI compared to healthy controls. No correlation between Cu and cognitive measures was found.	Rozzini et al. (2018)
56	Se	CSF	Italy	↓ Se in MCI patients.	Vinceti et al. (2019)
2068	Se	Whole blood	United States	↓ Se were associated with cognitive impairment.	Yan et al. (2020)
1006	Cu, Se, Zn	Whole blood	China	↑ Zn and ↓ Se and Cu bound to Zn or Se in MCI patients.	Yu et al. (2023)
333	Al, As, Cd, Cu, Fe, Mo, Ni, Rb, Sb, Se, Sn, Sr	Plasma	China	↑ Al, ↑ Cd and ↑ Cu were associated with elevated risk of cognitive impairment	Zhang et al. (2022)

AD: Alzheimer's Disease, CSF: cerebrospinal fluid, MCI: Mild Cognitive Impairment.

levels (Se_t) were observed in comparison to healthy controls (56,36 μg/L vs. 76,96 μg/L, $P < 0,001$, respectively; Nascimento et al., 2021). Furthermore, there was a significant positive correlation between Se_t and the risk of developing AD. The same results were obtained in other populations, such as in 82 Taiwanese AD patients (Yang et al., 2018) or in the serum of European AD patients (Ashraf et al., 2019; Socha et al., 2021; Vinceti et al., 2019). More specifically, the team of Vaz et al. (2018) observed that plasma Se concentration was reduced in advanced stages of the disease. Similarly, Yu et al. (2023) reported low blood Se levels in 211 MCI patients.

On the other hand, an analysis of the nails and hair of 40 AD patients found elevated Se levels (Koseoglu et al., 2021). These authors reported alterations in selenoprotein levels (decreased selenocysteine and increased selenomethionine) in their patients, probably due to genetic and metabolic differences, but further studies are needed to determine the cause of these differences. In contrast, Cardoso et al. (2019) found no significant differences in Se serum and CSF levels in Australian patients affected by MCI and AD.

In addition, there is some controversy regarding Se supplementation. In a randomised, double-blind clinical trial in 79 AD patients supplemented with Se and a probiotic for 12 weeks, cognitive and metabolic improvements were reported (Tamtaji et al., 2019). Similar results were obtained by Li et al. (2019b) where Se supplementation was associated with a decrease in cognitive symptoms. However, in another study of Italian AD patients, long-term Se supplementation was associated with an increased risk of developing the disease (Adani et al., 2020).

3.1.4. Zinc

The role of Zn in the development of AD and MCI is unclear and has led to controversial results. Zn concentrations decrease with age, leading to increased oxidative stress, inflammatory processes, and memory loss (Ashraf et al., 2019). Socha et al. (2021) found low Zn concentrations observed in serum of women with AD. On the other hand, Yu et al. (2023) found elevated Zn concentrations in the blood of Chinese MCI patients, especially in women. These authors suggested that the observed sex differences might be related to estrogen production after menopause, or to different consumption patterns in the countries studied. Other the link between a high intake of Zn with AD (Leko et al., 2021) and an increased cognitive impairment (Li et al., 2019b) has been

stated.

In contrast, Giacconi et al. (2019) and Yadav et al. (2021) reported decreased levels of Zn in plasma of AD patients without significant changes in MMSE. This apparent contradiction may be explained by the fact that Zn levels are likely to promote the formation of amyloid plaques at low concentrations. At the same time, they participate in Tau protein phosphorylation at high concentrations, both hallmarks of AD (Socha et al., 2021).

3.1.5. Other highly toxic metals and trace elements in AD and MCI

The Agency for Toxic Substances and Disease Registry (ATSDR) added Cd, Pb, As, and Hg to its Substance Priority List 2022 as four of the most toxic elements harmful to human health, even at low concentrations (ATSDR, 2022). Some authors have studied their relationship with the aetiology of MCI and AD.

In the case of Cd, some studies have linked high levels of concentration in blood to a decrease in cognitive functions (Li H. et al., 2018; Liu H. et al., 2021). Li H. et al. (2018) and Huang and Ren (2022) reported high Cd levels in 2068 and 467 American elders with low cognitive performance over 60 years of age, respectively. Similarly, Liu H. et al. (2021) found associations between high Cd concentrations and worse scores on various cognitive tests in a three-year longitudinal study in an elderly Chinese population. Another Chinese study reported an association between high Cd levels and cognitive impairment (Peng et al., 2020). More specifically, high Cd concentrations were found in AD patients (Yadav et al., 2021). Contrary to these results, Yang et al. (2018) did not detect differences in Cd levels in Taiwanese AD patients. The main sources of Cd exposure are food and tobacco smoke, the latter being a risk factor for AD (Cabrera et al., 2021). In addition, Cd can cross the BBB and is able to promote phosphorylation of the Tau protein, another hallmark of AD.

On the other hand, Pb shows more contradictory results. Fathabadi et al. (2018) found an increased Pb concentration in the blood of AD patients. However, some studies did not detect Pb in blood or serum of AD patients (Yadav et al., 2021; Yang et al., 2018). In a comparison between healthy controls, MCI patients, and patients with dementia compatible with AD, no differences in Pb levels were observed (Pinto et al., 2019). Lead may be involved in the formation of β-amyloid plaques by promoting the expression of the APP gene, leading to memory loss, impaired learning ability, and neuronal deterioration.

Regarding As, studies have been conducted in very heterogeneous matrices. In a study of AD patients and healthy controls, elevated urinary inorganic As concentrations were associated with an increased risk of AD (Yang et al., 2018). Koseoglu et al. (2021) reported high As concentrations in the nails and hair of AD patients. However, a study of 266 MCI patients showed no significant difference in As levels between patients and controls (Jakubowski et al., 2021). Yadav et al. (2021) also observed no change in As levels. It should be noted that interest in As is increasing in recent years, and further studies are likely to complement these preliminary data.

Mercury is one of the most harmful toxins to humans. Continued exposure to Hg causes multiple disorders even at low concentrations. In one study, elevated levels of Hg were found in blood of AD patients (Yadav et al., 2021). Similarly, higher concentrations of Hg were found in hair of dementia patients compared to MCI patients, and of MCI patients compared with healthy controls (Pinto et al., 2019). In contrast, Yang et al. (2018) reported no differences in Hg levels in AD patients.

Other trace elements studied were Ca and Mg. It has been observed that plasma Ca concentration in AD patients was much lower than in the control group (Ashraf et al., 2019). Reductions of Ca level in CSF of AD patients have also been described in association with Fe deposition in the brain (Jouini et al., 2021). Controversially, Leko et al. (2021) reported an increase in plasma Ca that was associated with individuals carrying the ε4 allele of the APOE gene. APOE is a modulator of Ca concentration, so Ca dyshomeostasis may be closely related to AD. Elevated Mg concentrations were also correlated with MCI and AD patients carrying APOE4 (Leko et al., 2021). However, these results were not replicated in CSF from AD patients (Jouini et al., 2021). Further studies are needed to understand the role of both trace elements in the aetiology of AD.

Finally, Al follows trends observed for other metals. The association between Al and the development of AD has been known for a long time. A causal analysis study demonstrated that chronic Al intake causes AD (Walton, 2014). Yadav et al. (2021) detected elevated Al levels in the blood of AD patients. This increased Al concentration has been reported in the nuclei of nerve cells in the brains of individuals with AD, colocalising with Fe deposition (Yumoto et al., 2018). This accumulation causes dysregulation of iron homeostasis and microtubule depletion, leading to the loss of functionality of these cells observed in the brains of AD patients (Walton, 2014). More interestingly, Jakubowski et al. (2021) noted that Al is negatively associated with attention and processing speed. However, Cabral Pinto et al. (2019) found no differences in Al concentration in the nails of healthy controls, MCI patients, and dementia patients.

3.2. Lewy Bodies dementias: Lewy Bodies dementia (LBD) and Parkinson disease dementia (PDD)

Lewy Bodies dementias is an umbrella term that includes LBD and PDD. Some autors have discussed whether these are different forms of the same pathology (Walker et al., 2015). Although LBD and PDD have very similar clinical symptomatology, our search did not show any articles focused on LDB. The most studied highly toxic metals and trace elements in Parkinson's disease (PD, with and without dementia) were Fe (9 articles), Zn (6 articles), Mn (5 articles), and Cu (4 articles). References to Ca, Hg, As, Pb, and Se were less abundant (1 article each). Table 3 shows the articles included in this review.

3.2.1. Iron

The relationship between Fe and the aetiology of PDD is controversial. Numerous studies have reported that elevated Fe levels correlate with an increased incidence of PDD (Guan et al., 2019; Pesch et al., 2019; Thomas et al., 2020). In a study using UK Biobank data, a positive relationship between Fe supplementation and the occurrence of PDD was observed (Takeuchi and Kawashima, 2022). Most of the Fe is deposited in the substantia nigra, causing degeneration of dopaminergic neurons, and leading to the classic symptomatology of PDD. This neuronal death may be related to increased α-synuclein aggregations and decreased ceruloplasmin, leading to high oxidative stress (Guan et al., 2019). These are not the only brain areas with Fe accumulation: in a study of 35 PD patients, increased Fe concentrations in the globus pallidus were found to correlate positively with motor dysfunctions typical of the disease (Pesch et al., 2019).

Fe deposition has also been studied by quantitative susceptibility mapping (QSM). Uchida et al. (2019) analysed Fe levels in different brain areas of 24 PDD patients, obtaining elevated Fe values that correlated negatively with Montreal Cognitive Assessment (MoCA) scores. This cognitive battery comprises tests of attention and visuospatial skills, verbal, and visual memory, which lower scores are associated with greater cognitive impairment. Consistent with these results, another study reported a relationship between Fe deposition and gene expression in astrocytes and glutamatergic neurons (Thomas et al., 2021). The overexpressed genes are involved in metal detoxification processes and synaptic function, which is consistent with the increased presence of Fe and the need to reduce its levels.

Other studies obtained completely different results. Ajsuvakova et al. (2020) detected no changes in total Fe concentration between PD patients and healthy controls in hair, serum, and urine samples. They also reported no changes when performing speciation analysis. Similar results were obtained in CSF and total plasma, with no differences detected even after speciation analysis (Willkommen et al., 2018). This lack of results may be due to the inclusion of PD patients without

Table 3
Summary of Parkinson's Disease Dementia studies with their most relevant goals.

Number of samples	Metals studied	Matrix	Country	Results	Reference
13	Cu, Fe, Mn, Zn	Serum Urine Hair	Russia	Species of Cu and Mn differed from PD patients to healthy controls.	Ajsuvakova et al. (2020)
187	Mn	Airborne	South Africa	Signs of parkinsonism were associated with Mn exposure in mine workers.	Dlamini et al. (2020)
26	Ca, Fe, Zn	Hair	Brazil	↓ Ca, Fe was found in PD patients. ↑ Zn was found in PD patients.	Dos Santos et al. (2018)
22	Ca, Fe, Zn	Hair	Brazil	↑ Zn was associated with depression and psychotic symptoms in PD patients.	Dos Santos et al. (2019)
90	Fe	Brain imageing	China	↑ Fe-related nigral degeneration disrupts functional connectivity between bilateral striatums in PD patients.	Guan et al. (2019)
50	Cu	Serum	Russia	↓ Cu was related to PD development and predominantly affected the non-motor symptoms of PD.	Ilyechova et al. (2018)
325	Cu, Fe, Zn	Serum	Republic of Korea	↓ Cu was related to PD, and it was negatively correlated with MMSE scores in PD patients.	Kim et al. (2018)
182	Mn	Airborne	United States	↑ Mn was related to a higher incidence of motor disorders and tremor without cognitive impairment.	Kornblith et al. (2018)
NA	As	Soil	Taiwan	PD prevalence was correlated with farm soil As levels in Taiwan.	Lee et al. (2021)
75	Se	CSF	Germany	Selenium speciation assay reported no significant differences between PD patients and healthy controls.	Maass et al. (2020)
61	Zn	Serum	Japan	Frequent levodopa administration strongly influenced Zn levels which may have alleviating effects on psychiatric symptoms.	Matsuyama et al. (2021)
4	Hg	Brain	United States	↑ Hg was associated with several PD symptoms in PD patients.	Pamphlett and Bishop, 2022
1528	Pb	DNA methylation	United States	Long-term Pb exposure tracked via DNA methylation may contribute to PD pathogenesis.	Paul et al. (2021)
35	Fe	Brain imageing	Germany	Motor dysfunction in PD correlates with alterations in brain Fe and neurometabolites.	Pesch et al. (2019)
621	Mn	Airborne	South Africa	Environmental airborne Mn exposures may be associated with clinical parkinsonism.	Racette et al. (2021)
911	Fe	Serum	United Kingdom	↑ Fe intake may increase parkinsonism risk.	Takeuchi and Kawashima, 2022
100	Fe	Brain imageing	United Kingdom	↑ Fe in brain was associated with increased PD risk.	Thomas et al. (2020)
96	Fe	Brain imageing	United Kingdom	Genes differentially expressed in PD were associated with the Fe accumulation pattern in brain.	Thomas et al. (2021)
24	Fe	Brain imageing	Japan	↑ Fe was associated with cognitive impairment in PD.	Uchida et al. (2019)
33	Cu, Fe, Mn, Zn	CSF	Germany	Speciation analysis didn't show differences in metal levels in PD patients.	Willkommen et al. (2018)

CSF: cerebrospinal fluid, MMSE: Mini Mental State Examination, NA: Not available, PD: Parkinson's Disease.

cognitive impairment. Another study in 325 PDD patients also reported no change in total Fe concentration (Kim et al., 2018). Future research is needed to determine the true nature of the relationship between Fe and PDD.

3.2.2. *Zinc*

Despite being one of the most studied essential trace elements, the available data on Zn seem to indicate contradictory relationships. Kim et al. (2018) described a decrease in serum Zn concentration in PD patients positively associated with age. However, this decrease did not correlate with MMSE scores. Controversially, in a hair study of 26 PDD patients, elevated Zn levels were detected in older individuals (Dos Santos et al., 2018). Later, the same research group reported the correlation between high Zn concentration and the presence of depression and psychotic symptomatology in their PD patients (Dos Santos et al., 2019). This reinforces the idea that Zn may play a role in the development of hallucinations, delusions, and paranoia, which are common in this type of patient.

The relationship of Zn with Zn-chelating drugs, such as levodopa, a metabolic precursor of dopamine, has been studied. Levodopa is the most widely used drug in the treatment of PD and has a negative correlation with Zn concentration (Matsuyama et al., 2021). Although abuse of these drugs can lead to Zn deficiencies, decreasing Zn concentration helps to alleviate psychotic symptomatology, which is consistent with the results obtained by Dos Santos et al. (2019).

However, other studies have found no difference in Zn levels in PD patients compared to healthy controls, measured in urine, hair, serum, and CSF (Ajsuvakova et al., 2020; Willkommen et al., 2018).

3.2.3. *Manganese*

The relationship of Mn with PD is close, as manganism or Mn deficiency presents very similar motor symptomatology (Kornblith et al., 2018). Numerous studies have reported increases in Mn concentration associated with an increased incidence of PD (Dlamini et al., 2020; Racette et al., 2021). Ajsuvakova et al. (2020) found elevated concentrations of Mn bound to albumin (Mn-albumin) in PD patients.

Another aspect that has attracted the interest of the scientific community is occupational exposure to Mn. A study in South African miners revealed high levels of Mn that correlated with higher scores on the Unified Parkinson's Disease Rating Scale (UPDRS, Dlamini et al., 2020). Higher scores on the UPDRS indicates a greater severity of PD symptoms. The same group reported increased incidence of motor symptoms in another group of 621 miners related to high concentrations of Mn in particulate matter ($PM_{2.5}$-Mn, Racette et al., 2021). Similar results were obtained by Kornblith et al. (2018) where Mn concentration was related to a higher incidence of motor disorders and tremor without cognitive impairment. These authors highlight the importance of separating the motor symptomatology caused by Mn exposure from the motor symptomatology of PD, as they argue that they may have different pathophysiology. Therefore, further studies are needed to elucidate the true role of Mn in the aetiology of PD.

In contrast, a study of Mn concentration in total plasma and CSF of PD patients reported no significant changes (Willkommen et al., 2018). This phenomenon can be attributed to the ability of Mn, bound to low molecular weight molecules such as citrate (Mn-citrate), to permeate the BBB and subsequently accumulate within the basal ganglia.

It is worth noting that the studies did not consider the cognitive

status of PD patients, thereby presenting a challenge in evaluating the impact of Mn on the development of dementia in this disease.

3.2.4. Copper

The possible role of Cu in the aetiology of PD is unclear. Ajsuvakova et al. (2020) found no significant difference between serum total Cu levels of PD patients and healthy controls. However, when performing speciation analysis, they found that the Cu/Cp ratio was reduced in PD patients. This indicated that Cu ions did not bind to Cp, but to other low molecular weight species (mainly Cu-binding amino acids) or free Cu. Free Cu can activate oxidative stress mechanisms and reactive oxygen species (ROS), as well as bind to alpha-synuclein aggregates and lead to neuronal degeneration. Similar results were obtained by Willkommen et al. (2018) whose PD patients had a higher concentration of Cu bound to amino acids.

In another study with 50 Russian PD patients, concentrations of serum Cu, Cp, and other related metabolites were calculated and found to be reduced compared to controls (Ilyechova et al., 2018). This generalised reduction in Cu metabolism correlated positively with non-motor symptomatology of the disease.

Consistent with this work, Kim et al. (2018) described low serum Cu concentrations correlated with the presence of PD. However, the same authors found that Cu concentration was negatively related to MMSE scores, which are indicative of cognitive impairment and non-motor symptomatology associated with the disease. Lower MMSE scores are generally associated with greater cognitive decline. Further studies would be needed to verify the results obtained.

3.2.5. Other highly toxic metals and trace elements in PD

As mentioned above, As, Hg, and Pb are on the ATSDR Substance Priority List 2022; ATSDR 2022). All three are considered extremely toxic even at low concentrations, so some studies have tried to elucidate their role in the development of PD.

Lee et al. (2021) studied As exposure and the prevalence of PD in different areas of Taiwan using national surveys, finding a significant association between them. Interestingly, the three areas with the highest prevalence of PD corresponded to areas with the highest As soil contamination, so occupational As exposure is strongly related to the development of PD. Arsenic is capable of forming α-synuclein aggregates in murine models that can give rise to the Lewy bodies typical of the disease.

Mercury can also aggregate with α-synuclein, colocalising with Lewy bodies and in neurons and oligodendrocytes in affected brain regions of PD patients, such as the substantia nigra (Pamphlett and Bishop, 2022). Furthermore, these researchers observed a relationship between Hg accumulation and different motor symptoms of the disease.

In the case of Pb, elevated concentrations were found in the tibia of PD patients (Paul et al., 2021). Tibial Pb is measured using mitochondrial DNA biomarkers, which is more reliable than self-reporting by patients.

Other elements that may be relevant in the development of PD include Ca and Se. Dos Santos et al. (2018) found reduced Ca concentrations in the hair of PD patients compared to healthy controls. Ca can bind to alpha-synuclein causing conformational changes that facilitate its conversion to Lewy bodies, as well as generating oxidative stress and neurodegeneration. This binding may be favored by disruptions of the BBB, which would allow for a greater accumulation of Ca in brain regions. Despite this, the relationship between calcium and Lewy bodies requires further investigation. On the other hand, Maass et al. (2020) collected CSF samples from PD patients and performed a Se speciation assay, finding no significant differences between groups.

3.3. Frontotemporal dementia (FTD)

The highly toxic metals and trace elements studied were Cu, Fe, Al and Se, with 1 reference each (Table 4). Despite being one of the most prevalent dementias, FTD has been less studied than the previous ones. This dementia appears in the lifespan few years earlier than others and has several subtypes. The best known are the behavioural variant (bvFTD), which affects behaviour, and the aphasic variant (PPA), which affects language.

In a study of 45 Italian bvFTD patients and 35 PPA patients, serum Cu and Cp concentrations were measured against healthy controls (Squitti et al., 2018). None of the markers of Cu metabolism showed statistically significant differences, unlike in AD. Another study by the same group sought to characterise the metabolic profile of Fe and its relationship with serum Cu levels (De Luca et al., 2020). Although a reduction in the Cp activity of FTD patients was described, the differences were not significant. This reduction suggests a dyshomeostasis of Fe, considering the role of Cp in Fe transport and oxidation.

On the other hand, the group of Adani et al. (2020) found an increased risk of FTD associated with occupational Al exposure. They also described long-term Se supplementation as a risk factor for the development of FTD and AD. However, due to the low number of cases (19 FTD patients), they concluded that further studies with larger samples were needed to validate these initial observations.

3.4. Metals, cognition, and gut microbiota

Literature focusing on the role of metals in dysbiosis of the GMB and cognition in elderly is scarce. The search conducted in this review just shows 3 articles, which are mainly focused on Pb, Cd, and Fe (Table 5).

Eggers et al. (2019) performed a cross-sectional population-based sample study to determine the effects of Pb exposure in GMB. High levels of urinary Pb were associated with increases in richness and α-diversity in elders. It is generally accepted that a healthy GMB will exhibit higher values of α-diversity (Walters and Martiny, 2020). Furthermore, differences in β-diversity were detected, with increases in the concentration of Proteobacteria (specifically Burkholderiales). Beta diversity quantifies the variability in the composition of a community (the identity of observed taxa), and higher values are often associated with healthy states of GMB. On the other hand, elevated abundances of Proteobacteria have been described in Chinese AD patients (Liu P. et al., 2019). These findings suggest that exposure to Pb can result in a decrease in the population of bacteria that are highly abundant, thus disrupting the evenness of abundance across all taxonomic groups. Probably, Pb acts as growth regulator of certain bacterial groups that would otherwise not grow. However, metals have antibiotic activity that could affect the

Table 4
Summary of Frontotemporal Dementia studies with their most relevant goals.

Number of samples	Metals studied	Matrix	Country	Results	Reference
19	Al, As, Cd, Hg, Pb, Se	Self-administered questionnaire	Italy	↑ Al was associated with FTD. ↑ Se supplementation was associated with FTD.	Adani et al. (2020)
34	Fe, Cu	Serum	Italy	↓ Cp activity in FTD patients suggests a dyshomeostasis of Fe.	De Luca et al. (2020)
45	Cu	Serum	Italy	Analysis didn't show differences between FTD patients and healthy controls.	Squitti et al. (2018)

Cp: ceruloplasmin, FTD: Frontotemporal Dementia.

Table 5
Summary of metals, microbiota, and cognition studies with their most relevant goals.

Number of samples	Metals studied	Matrix	Country	Results	Reference
57	Fe	Stool	United Kingdom	↑ Fe supplementation was associated with low levels of esters and SCFA-producing bacteria.	Ahmed et al. (2020)
466	Pb	Urine Stool Serum	United States	↑ Pb in urine was associated with increases in richness, α-diversity and Proteobacteria in elders.	Eggers et al. (2019)
NA	Cd	Soil Gastric solutions	China	↑ Cd was associated with low bacterial total abundance.	Guo et al. (2022)

NA: Not available, SCFA: Short-chain fatty acids.

GMB (Eggers et al., 2018).

On the other hand, high concentrations of Cd were correlated with decreases in bacterial total abundance (Guo et al., 2022). In mice, elevated Cd conducted to reductions of anaerobic bacteria and *Lactobacillus* and increases of *Lachnospiraceae*, which are related to inflammatory response in the gut (Jafarpour et al., 2015; Breton et al., 2013). The *Lachnospiraceae* family has been described on several occasions for its relationship with PD. Multiple studies agree that patients with PD show decreased abundance of *Lachnospiraceae*, which is associated with rapid cognitive decline (Barichella et al., 2019; Li et al., 2019a).

Finally, Fe supplementation was associated with low levels of esters and decreases in SCFA-producing bacteria, like Firmicutes or *Faecalibacterium prausnitzii* (Ahmed et al., 2020). Both observations reflect the suppression of intestinal bacteria, which could lead to dysbiosis. Specifically, reduced abundances of *Faecalibacterium* have been associated with pro-inflammatory states typically observed in MCI and PD (Keshavarzian et al., 2015; Ueda et al., 2021).

In summary, due to the lack of studies in this area, further articles are needed to elucidate the effects of metals on cognition through the GMB.

4. Conclusions and future recommendations

Metals play a key role in the development of different forms of dementia, which has been demonstrated by the large number of studies reporting associations between concentrations of them and dementia.

In our review, high levels of Fe and Cu seem to be related to the development of MCI and AD. In turn, low concentrations of Se are associated with poor cognitive status. However, the role of Zn in AD is controversial and further studies are needed.

On the other hand, elevated concentrations of Fe, Mn and Zn have been found in patients with PDD. In contrast, studies in Cu do not shed light on the aetiology of PDD. Further studies are needed in relation to LBD to elucidate whether metals may be related to the disease.

Finally, exposure to high levels of Al is associated with FTD development. Similarly, elevated Se concentration seems to be associated with the onset, but more investigation is needed.

The heterogeneity of the matrices studied in metal analysis and the variability of analytical techniques make it difficult to compare studies. The number of subjects studied is another limitation, so it would be necessary to replicate results in larger cohorts.

In conclusion, there is a clear gap in understanding the influence of metals on cognition through the GMB. Further studies are needed to confirm its potential relevance, particularly considering new findings regarding the role of microbiota in the symptomatology of these diseases. Additionally, it is crucial to investigate other environmental (besides metals) and individual factors in determining cognitive disorders and GMB in the elderly.

Credit author statement

David Mateo: Conceptualization, Investigation, Writing – original draft. Montse Marquès: Conceptualization, Writing – review & editing, Supervision. Margarita Torrente: Conceptualization, Writing – review & editing, Supervision, Project administration.

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Data availability

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Glossary

Abbreviation Definition

AD: Alzheimer's disease
Al: Aluminium
As: Arsenic
ATSDR: Agency for Toxic Substances and Disease Registry
BBB: Blood-brain barrier
bvFTD: Frontotemporal dementia behavioural variant
Ca: Calcium
Cd: Cadmium
CI: Confidence interval
CNS: Central Nervous System
Cp: Ceruloplasmin
Cp-Tf: Ceruloplasmin-transferrin
CSF: Cerebrospinal fluid
Cu: Copper
Fe: Iron
FTD: Frontotemporal dementia
GMB: Gut microbiota
Hg: Mercury
LBD: Lewy Bodies dementia
MCI: Mild cognitive impairment
Mg: Magnesium
MMSE: Mini-Mental State Examination Test
Mn: Manganese
Mn-albumin: Manganese bound to albumin
OR: Odds ratio
Pb: Lead
PD: Parkinson's disease
PDD: Parkinson's disease dementia
PM: Particulate matter
PPA: Frontotemporal dementia aphasic variant
QSM: Quantitative susceptibility mapping
ROS: Reactive oxygen species
SCFA: Short-chain fatty acids
Se: Selenium
Se_i: Erythrocyte selenium
UPDRS: Unified Parkinson's Disease Rating Scale
WHO: World Health Organization
Zn: Zinc