Exposure and Health (2026) 18:32
https://doi.org/10.1007/s12403-026-00769-w

ORIGINAL PAPER

Association Between Heavy Metal Exposure and Alzheimer's Disease Prevalence and Mortality: A Systematic Review and Meta-analysis

Yaohui Fang[1,2] · Huma Shahzad[1,2] · Zhi Li[1,2] · Jiarong Zhang[1,2] · Xinru Wang[1,2] · Ziyan Qiao[1,2] · Hong Qian[1,2] · Qiaoqiao Xu[1,2] · Yun Fan[1,2,3] · Chuncheng Lu[1,2]

Received: 2 November 2025 / Revised: 11 March 2026 / Accepted: 22 March 2026

Abstract
Exposure to heavy metals, namely cadmium, arsenic, lead, mercury, together with manganese, has been increasingly implicated in the prevalence and mortality of Alzheimer's disease. To further clarify these associations, we conducted a comprehensive meta-analysis by systematically searching the Cochrane Library, PubMed, and Web of Science databases up to July 9, 2024. In total, 21 studies involving 2,867 participants were included for analyses using standardized mean differences, and 8 studies involving 288,737 participants were analyzed using odds ratios (ORs) or hazard ratios (HRs). Using a random-effects model with Stata 17.0, we found that cadmium levels in biological samples were higher in individuals with Alzheimer's disease relative to those without the condition (SMD = 0.99, 95% CI 0.40, 1.50). Similarly, arsenic levels were elevated among Alzheimer's disease patients relative to control groups (SMD = 0.66, 95% CI 0.02, 1.20). Moreover, higher cadmium exposure was associated with an increased risk of Alzheimer's disease–related mortality (HR = 1.80, 95% CI 1.20, 2.69). Evidence from this study suggests that elevated cadmium and arsenic levels were associated with the presence of Alzheimer's disease and that cadmium exposure, in particular, was associated with higher Alzheimer's disease-related mortality. These findings may have implications for public health monitoring and prevention strategies related to heavy metal exposure.

Keywords Alzheimer's disease · Heavy metals · Prevalence · Mortality

Introduction

Dementia results from a range of diseases and brain injuries, with Alzheimer's disease (AD) accounting for the bulk of cases, potentially resulting in 60–70% of all cases (World Health Organization 2021). It is a primary driver of disability and impairment among aging individuals on a global scale. It impairs memory, cognitive functions, and behavior, eventually hindering an individual's capacity to carry out everyday tasks (Nichols et al. 2022). Worldwide, dementia affects over 46 million people, among which Alzheimer's disease comprising approximately 70% of these cases (Qiu et al. 2009; Reitz et al. 2011).

Despite the high prevalence of this condition, effective treatment remains elusive (Scheltens et al. 2016; Livingston et al. 2020). Over the past several years, many mechanisms have been disclosed about the pathogenesis of AD. However, two hallmark pathological changes—amyloid beta peptide structuring and tau protein aggregation—are widely acknowledged, manifesting as extracellular plaque deposits

Yaohui Fang, Huma Shahzad and Zhi Li have contributed equally to this study and should be regarded as joint first authors.

✉ Yun Fan
yunfan@njmu.edu.cn

✉ Chuncheng Lu
chunchenglu@njmu.edu.cn

[1] State Key Laboratory of Reproductive Medicine, Center for Global Health, School of Public Health, Nanjing Medical University, Nanjing 211166, China

[2] Key Laboratory of Modern Toxicology of Ministry of Education, School of Public Health, Nanjing Medical University, Nanjing 211166, China

[3] Department of Microbes and Infection, School of Public Health, Nanjing Medical University, Nanjing 211166, China

Published online: 07 April 2026

in the brain and neurofibrillary tangles in the brain (Qiu et al. 2009; Yslas et al. 2024; Zhang et al. 2024). This highlights the growing demand for effective preventive strategies to reduce the occurrence of AD.

The hazard of AD is primarily linked to a synergy of hereditary and environmental factors (Livingston et al. 2020). The industrial development in developing countries has led to the release of toxic chemicals into the air, making reports of heavy metal exposure more common (Babić Leko et al. 2022). Heavy metals are recognized as causative and risk factors for various diseases. Notably, cadmium (Cd), lead (Pb), and arsenic (As) are particularly connected to neurotoxic effects (González-Domínguez et al. 2014; Wang et al. 2019; Eiró et al. 2021).

Cadmium is a toxic trace metal to humans, originating from natural as well as human-derived routes (Filippini et al. 2020). Among non-occupationally exposed individuals, nutrition and cigarette consumption are the original routes of exposure (Filippini et al. 2018). Conversely, lead sources include lead-containing paints, solder, bullets, ceramic goods, industrial discharges, contaminated food and water, soil, and substitute health products (Obeng-Gyasi 2019). Arsenic is also among the most significant hazardous elements in the environment, existing in both organic and inorganic forms. Arsenic can enter the human body through ingestion, inhalation, or dermal absorption, leading to various adverse health outcomes (Rahmani et al. 2023). Of course, the impacts of manganese and mercury on human health are also not to be overlooked. Manganese is a vital trace element for the human physique, but at elevated levels, it acts as a neurotoxin. It can pass into the body through ingestion, breathing in, and potentially through the olfactory pathway. Mercury exposure can originate from geogenic as well as anthropogenic sources. Human actions, including the combustion and the use of coal and oil, the chlor-alkali industry, mining, can introduce mercury into ecosystems, leading to mercury exposure (Paduraru et al. 2022). And finally, Manganese that circumvents the liver is readily penetrates the blood-brain barrier and accumulates localized to the basal ganglia (Racette et al. 2021).

Understanding environmental determinants for Alzheimer's disease can facilitate our comprehension of the disease's pathology, potentially influencing intervention strategies. Resulting from the limited availability of comprehensive reviews regarding this subject, our aim sought to carry out an integrative review and meta-analysis comparing the concentrations of five neurotoxic heavy metals in biological samples of Alzheimer's individuals and non-diseased controls. Additionally, recognizing that the link between heavy metals and Alzheimer's disease-related mortality and prevalence remain unclear, we conducted a second meta-analysis, incorporating eight studies from three major indexed sources, to assess the probability of Alzheimer's disease-related mortality and prevalence related to heavy metal exposure.

Method and Materials

Aiming to investigate the correlation between exposure to hazardous metals and Alzheimer's disease prevalence and mortality, the meta-analysis was conducted in accordance with PRISMA guidelines. Registration of the review protocol was completed in the PROSPERO database (CRD42024567068).

Study Eligibility and Criteria

A structured literature investigation was carried out, first in the Cochrane Library, then in PubMed, and finally in Web of Science for articles retrievable until July 9, 2024. Eligible studies comprised observational designs—case-control, cross-sectional, and cohort studies and needed to evaluate exposure to any of the following metals: lead, cadmium, arsenic, manganese, or mercury, while also reporting outcomes pertinent to Alzheimer's disease. The comprehensive search strategy, along with detailed eligibility criteria and the study selection process, is available in the *Supplementary Methods*.

Data Retrieval

Two reviewers independently extracted data, covering key study characteristics, among others the first author, year of publication, investigative design, subject characteristics, definitions of exposure and endpoints, and relevant effect measures. Consensus discussions resolved any discrepancies between reviewers.

Evaluation of Methodological Quality

We employed the Newcastle-Ottawa Scale (NOS) to appraise the credibility of cohort. The same scale was applied to assess the credibility of case-control studies. And for cross-sectional studies, we employed the tool from the U.S. Agency for Healthcare Research and Quality (AHRQ). Two researchers carried out these assessments independently.

Quantitative Analysis

The meta-analysis was carried out via Stata version 17.0 to synthesize the effect estimates. Effect estimates were synthesized according to their reported metric. Hazard ratios

(HRs) and odds ratios (ORs) were pooled separately and were not combined within the same model. Only adjusted effect estimates were included in the primary meta-analysis. The I^2 statistic quantified between-study heterogeneity, guiding the choice of either a random-effects or fixed-effects model to derive summary estimates. For meta-analyses including a very small number of studies, fixed-effects models were applied to avoid unstable estimation of between-study variance under random-effects assumptions (Dettori et al. 2022). To test the robustness of the findings, we undertaken sensitivity and subgroup analyses. Where appropriate, publication bias was evaluated. The *Supplementary Methods* section contains further specifics on the statistical approach.

Results

Study Selection

After removing 566 redundant articles, 1203 articles remained. Of these, 1147 articles were excluded for the following reasons: 186 articles involved animals, 165 articles were reviews, 614 studies were unrelated to the topic, 15 publications were clinical case studies, 10 articles were meeting abstracts, and 157 articles were studies on molecular mechanisms. An additional 14 articles were excluded due to insufficient statistical data, and 9 were omitted because their examined variables or results were unrelated. Ultimately, 27 articles were selected for additional analysis (see Supplementary Material Online, *Figure S1*). Data from 21 of these articles were combined to calculate standardized mean differences (SMD). For exposure–outcome analyses ($n=8$), effect estimates were synthesized according to their reported metric, with hazard ratios (HRs) and odds ratios (ORs) pooled separately. Data from two of these articles were utilized in both analyses (Park et al. 2014; Yang et al. 2018).

Summary of Study Features

The detailed data of the studies incorporated were presented in *Supplementary Tables 1 and 2*. A total of twenty-three case-control studies, with an additional three cohort studies, and a cross-sectional study were encompassed in our analysis. Among the 27 articles, 8 studies were carried out in Asia (4 in China, 2 in Korea, 2 in India), 9 studies were conducted in Europe (3 in Spain, 2 in Italy, 2 in Sweden, 1 in Germany, and 1 in Lithuania), and North America (USA) accounted for 7 studies. Additionally, one study was conducted in Oceania (Australia) and two studies were conducted in Turkey. It was worth noting that Turkey's geographical location straddles both Europe and Asia. Therefore, a dual classification was applied during the subgroup analysis of continents. Heavy metal concentrations were measured using various techniques, with the most common methods being inductively coupled plasma and atomic absorption spectroscopy. Most studies utilized the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association) criteria for diagnosing Alzheimer's disease (AD).

Evaluation of Quality

As determined by the NOS quality assessment, eighteen studies were assessed as having moderate quality, while nine were deemed to have high quality. A cross-sectional study was assessed using a quality evaluation instrument and received a score of 10.

Heavy Metals and Alzheimer's Disease

Cadmium (Cd)

Eleven studies quantified the detected concentrations of Cd in multiple types of biological samples, such as serum, blood, and plasma, among individuals with AD and control subjects.

Within the present study, a random-effects model compared Cd concentrations in a sample comprising 560 AD individuals with 694 normal individuals (11 studies). Observed outcomes demonstrated that cadmium content in AD individuals was evidently greater than that in the comparator group, the overall SMD for cadmium concentration was 0.99 (95% CI 0.40, 1.5) (Fig. 1A). A random-effects model was employed to analyse the overall result; the I^2 *statistic* was 95.0% and the *P-value* was less than 0.001. The study also implemented a sensitivity analysis to assess the robustness and possible bias within the dataset by systematically by sequentially removing one study at a time. Begg's test indicated no significant publication bias ($z=1.87$, $p=0.062$). Egger's regression test yielded a borderline result ($p=0.050$), suggesting possible small-study effects; however, the evidence was insufficient to conclusively indicate substantial publication bias.

Subgroup analyses based on geographical location revealed markedly elevated Cd concentrations in AD individuals versus non-diseased participants in studies conducted in Asia (SMD = 1.43; 95% CI 0.43, 2.42; I^2=97.4%, $p<0.001$) and in Europe (SMD = 0.56; 95% CI 0.20, 1.58; I^2=56.1%, $p=0.059$), suggesting that the heterogeneity may be partially attributed to the inclusion of European studies. Additionally, subgroup analyses by sample type showed that Cd levels in the serum of AD individuals were

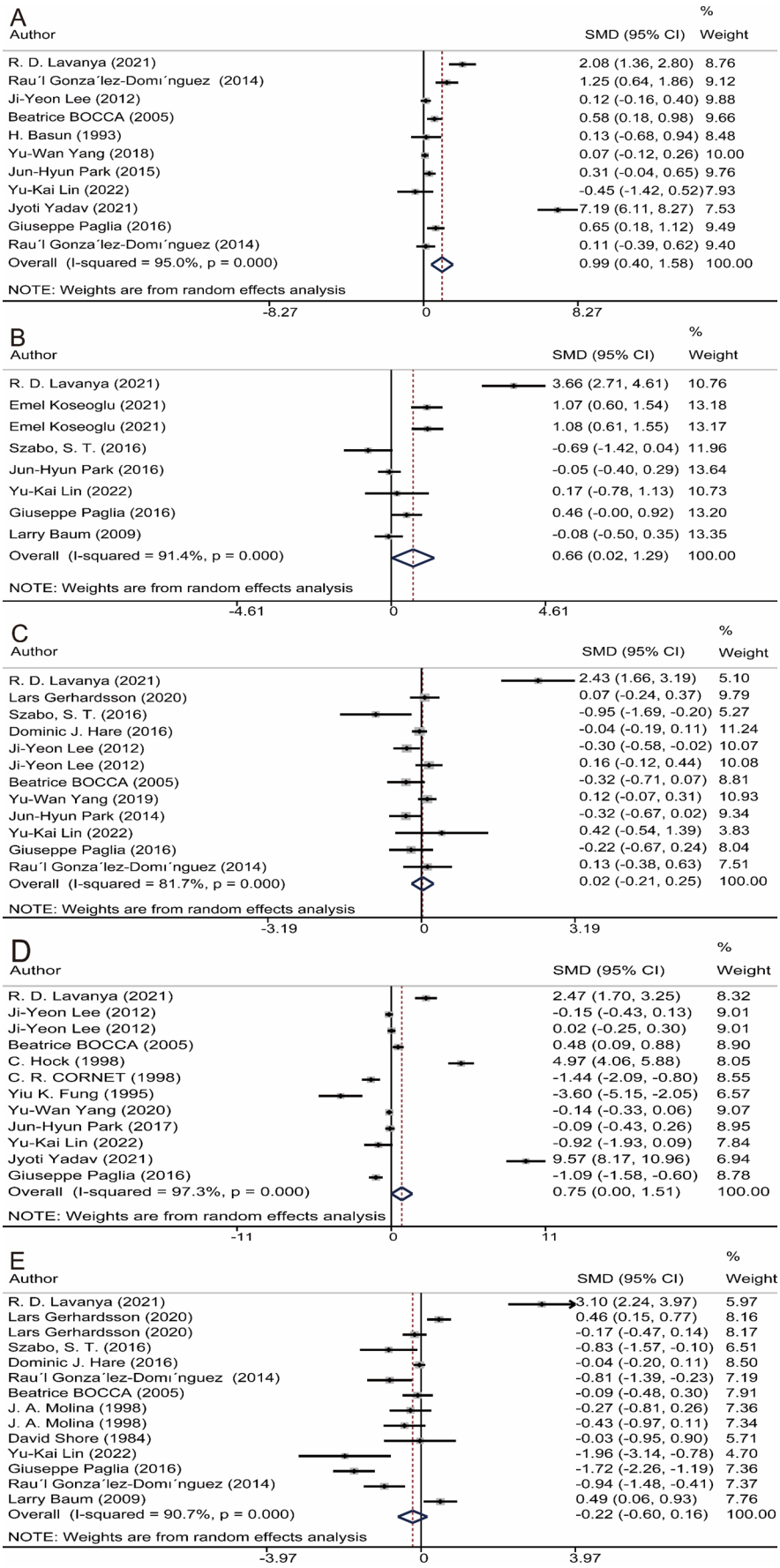

Fig. 1 Forest map of the relationship between heavy metals in different biological samples and Alzheimer's disease. **A** Point estimate and pooled estimate of Cd concentration in AD patients compared with healthy controls. **B** Point estimate and pooled estimate of As concentration in AD patients compared with healthy controls. **C** Point estimate and pooled estimate of Pb concentration in AD patients compared with healthy controls. **D** Point estimate and pooled estimate of Hg concentration in AD patients compared with healthy controls. **E** Point estimate and pooled estimate of Mn concentration in AD patients compared with healthy controls. CI: confidence interval; SMD: the standard mean difference

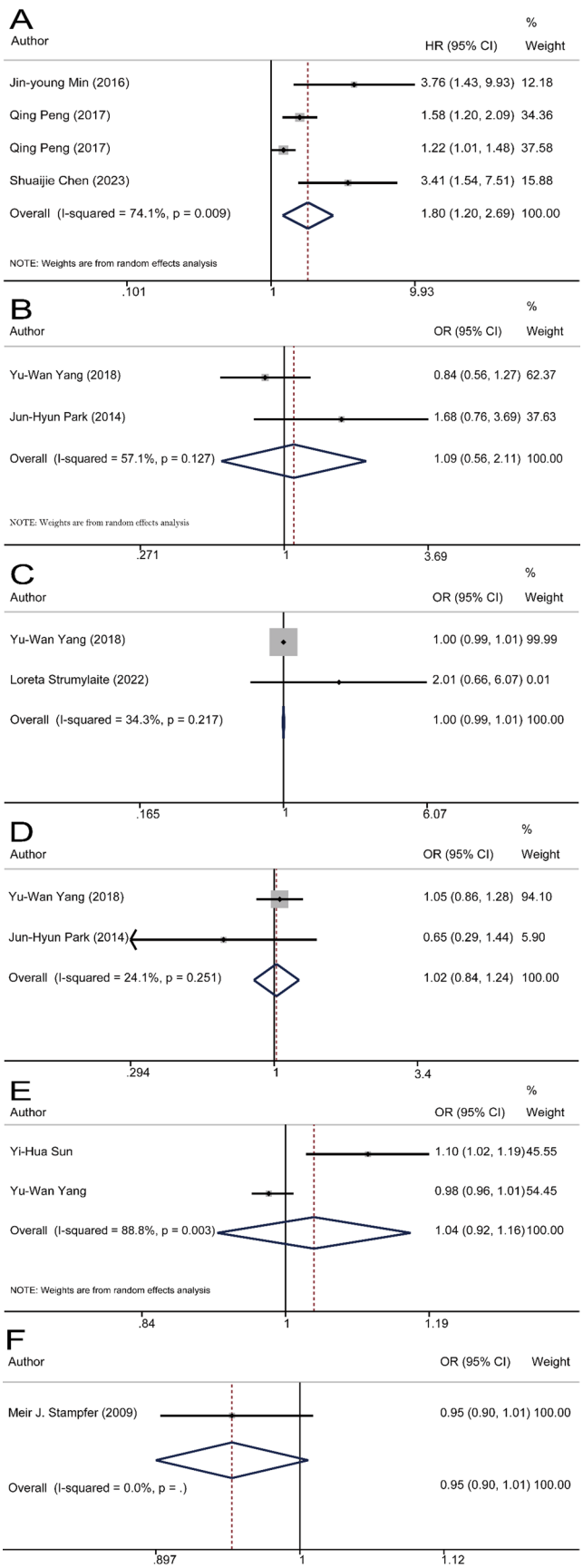

Fig. 2 Forest map of the association between heavy metal exposure and Alzheimer's disease. **A** Forest map of the association between cadmium exposure and Alzheimer's disease mortality. **B** Forest map of the association between cadmium exposure and Alzheimer's disease prevalence. **C** Forest map of the association between arsenic exposure and Alzheimer's disease prevalence. **D** Forest map of the association between lead exposure and Alzheimer's disease prevalence. **E** Forest map of the association between mercury exposure and Alzheimer's disease prevalence. **F** Forest map of the association between manganese exposure and Alzheimer's disease mortality. CI: confidence interval; HR: hazard ratio; OR: odds ratio

elevated relative to levels recorded in the comparator group (SMD = 0.77; 95% CI 0.32, 1.23; I^2=81.4%, p<0.001). Additionally, a subgroup analysis utilizing assessment methods indicated notable variances in Cd concentrations among the inductively coupled plasma mass spectrometry (ICP-MS) methods (SMD = 0.63; 95% CI 0.21,1.05; I^2 = 82.8%, p<0.001), while no notable differences were observed with the other two methods. The subgroup results based on the criteria for AD diagnosis showed that the cadmium concentration in the case group diagnosed by NINCDS-ADRDA criteria was markedly greater than those relative to non-demented participants (SMD = 1.37; 95% CI 0.37, 2.36; I^2 = 96.1%, p<0.001). The outcomes were outlined in *Supplementary Table 3*.

In addition, the pooled analysis of three cohort studies indicated a robust positive correlation between exposure to cadmium and Alzheimer's disease-related mortality (HR = 1.80; 95% CI 1.20, 2.69) (Fig. 2A), with substantial heterogeneity (I^2=74.1%, p = 0.009). Similarly, we conducted a sensitivity analysis, providing evidence that our observed effects were robust. However, evidence from the pooled analysis of two case-control studies did not support a significant association between exposure to cadmium and the prevalence of Alzheimer's disease (OR = 1.09; 95% CI 0.56, 2.11) (Fig. 2B).

Arsenic (As)

Seven researches quantified arsenic levels in a range of biological samples, including serum, blood, cerebrospinal fluid, as well as plasma, among AD patients and control groups.

As part of the meta-analysis, a random-effects model was implemented to compare arsenic (As) concentrations between 236 AD patients and 230 healthy individuals across seven studies. The observations indicated that the As concentration was pronounced superior in AD individuals than in the comparison group, with an overall SMD of 0.66 (95% CI 0.02, 1.2) (Fig. 1B). The overall analysis was conducted by means of a random-effects model; the I^2 *statistic* was 91.4%, with a *P-value* < 0.001. We additionally conducted a sensitivity analysis by systematically eliminating data from respective study to characterize the robustness and potential

bias of the observations. Owing to the inclusion of fewer than ten inquiries, no analysis of publication bias was carried out in this study.

The outputs of the subgroup analysis revealed that studies conducted in Asia found significantly higher arsenic content of biological samples of AD individuals relative to the reference group (SMD = 0.92; 95% CI 0.12, 1.71; I^2=93.0%, p < 0.001). Similarly, the subgroup analysis also revealed that studies conducted in Europe found significantly higher arsenic content of biological samples of AD patients relative to the comparator group (SMD = 1.08; 95% CI 0.74, 1.41; I^2=55.6%, p = 0.105). However, studies conducted in North America did not find significance. These results suggest that the heterogeneity of the study may be due to European versus North American literature. In other subgroup analyses, only the grouping based on measurement methods showed significant results. The data could be found in *Supplementary Table 4*.

Additionally, In the pooled analysis of the two case-control studies, no substantial association was detected between arsenic exposure and the prevalence of Alzheimer's disease (OR = 1.00; 95% CI 0.99, 1.01) (Fig. 2C). The heterogeneity across studies was low and not statistically significant (I^2=34.3%, p = 0.217).

Lead (Pb)

Eleven studies quantified lead levels in a variety of biological samples, including serum, blood, cerebrospinal fluid, along with plasma, in Alzheimer's patients and comparison group.

The meta-analysis incorporated a random-effects model to compare lead concentrations in 871 Alzheimer's disease individuals and 1,429 served as comparison group from 11 studies. The outcomes indicated that lead levels were greatly higher in AD individuals than in comparison group, with an overall SMD of 0.02 (95% CI -0.2, 0.25) (Fig. 1C). A random-effects model was employed for the overall analysis. The I^2 was 81.7%, and the *P-value* was less than 0.001. We also analyzed publication bias, and the Begg's regression test proposed the absence of a publication bias (z=-0.07, p = 1.000), and Egger's regression test likewise showed no evidence of publication bias (p = 0.641).

In subgroup analysis, no significant results were found for any grouping method. However, the findings from our subgroup analysis suggest potential sources of variability, stemming either from studies conducted outside of Europe (I^2=23.6%, p = 0.270) or from exposure types other than plasma (I^2=0.0%, p = 0.493). *Supplementary Table 5* illustrated the results.

In a comprehensive analysis of two case-control studies, we did not find a noteworthy link between exposure to lead and the prevalence of Alzheimer's disease (OR = 1.02; 95% CI 0.84, 1.24) (Fig. 2D), with no significant heterogeneity (I^2=24.1%, p = 0.251). Therefore, we utilized the fixed-effects model for the analysis.

Mercury (Hg)

Eleven studies quantified mercury levels in a variety of biological samples, including serum, blood, hypophysis, plus plasma, in Alzheimer's patients and controls.

A random-effects model was adopted in the meta-analysis to compare mercury concentrations in 581 AD patients and 691 individuals without the condition from 11 studies. The results indicated no remarkable difference in mercury concentrations between AD cases and non-diseased group, with an overall SMD of 0.75 (95% CI -0.00, 1.51) (Fig. 1D). A random effects model was employed for comprehensive analysis, yielding an *I^2 statistic* value of 97.3% and a corresponding *P-value* < 0.001. The Begg's regression test found no indication of publication bias (z = 0.48, p = 0.631), and Egger's regression test likewise showed no evidence of publication bias (p = 0.227).

In subgroup analysis, we found that in studies conducted in Asia (SMD = 1.24; 95% CI 0.38, 2.10; I^2=88.4%, p < 0.001), AD patients had significantly greater mercury levels than normal participants. No substantial differences were emerged in studies on other continents. In addition, in the subgroup of exposure types, mercury amount in the circulatory system of people with AD was significantly higher than that of healthy people (SMD = 2.09; 95% CI 0.29, 3.89; I^2=98.7%, p < 0.001). For a detailed summary of the results, refer to *Supplementary Table 6*.

The results of one case-control study and one cross-sectional study exhibited a clear link between mercury exposure and the prevalence of Alzheimer's disease (OR = 1.04; 95% CI 0.92, 1.16) (Fig. 2E), with significant heterogeneity (I^2=88.8%, p = 0.003).

Manganese (Mn)

Twelve studies quantified manganese levels in a variety of biological samples, including serum, hair, cerebrospinal fluid, plus plasma, in Alzheimer's individuals and controls.

In conducting the meta-analysis, a random-effects model was used to compare manganese concentrations in 661 Alzheimer's disease patients and 1071 non-diseased individuals from 12 studies. No notable difference was observed in the results in manganese concentration between AD individuals and comparison group, with an overall SMD of -0.22 (95% CI -0.60, 0.16) (Fig. 1E). The random effects model was employed for the comprehensive analysis. The *I^2 statistic* yielded a value of 90.7%, with a corresponding

P-value less than 0.001. We also conducted an analysis of publication bias, and the Begg's regression analysis found no proof of publication bias ($z=1.09$, $p=0.274$), and Egger's regression test likewise showed no evidence of publication bias ($p=0.520$).

Among the diverse subgroup analyses conducted, it was observed that manganese concentrations exhibited a meaningful decrease in the AD case group versus the comparison group in the European study (SMD=-0.47; 95% CI -0.93, -0.02; I^2=88.4%, $p<0.001$). Whereas no statistically considerable differences were noted in other subgroup analyses. The results were depicted in *Supplementary Table 7*.

Regarding the meta-analysis with a case-control study, we did not report a considerable connection between manganese exposure and Alzheimer's disease mortality (OR=0.95; 95% CI 0.90, 1.01) (Fig. 2F). As only a single study was available for this analysis, a sensitivity analysis could not be carried out.

Sensitivity Analysis

To examine the potential bias of the outcomes, we excluded data from the study one at a time, performing a sensitivity analysis subsequently. Analysis results of the sensitivity analyses indicated that our findings were generally robust, except for the associations of arsenic and lead with Alzheimer's disease prevalence, which showed instability. The results of the sensitivity analysis can be found in Figs. 3 and 4.

Discussion

There is now substantial evidence demonstrating the correlation between heavy metal exposure and human autoimmunity, as well as neuroendocrine dysfunction. Moreover, numerous investigations have revealed an affiliation between exposure to heavy metal and a broad spectrum of diseases (Ohsawa 2009; Monastero et al. 2018; Bjørklund

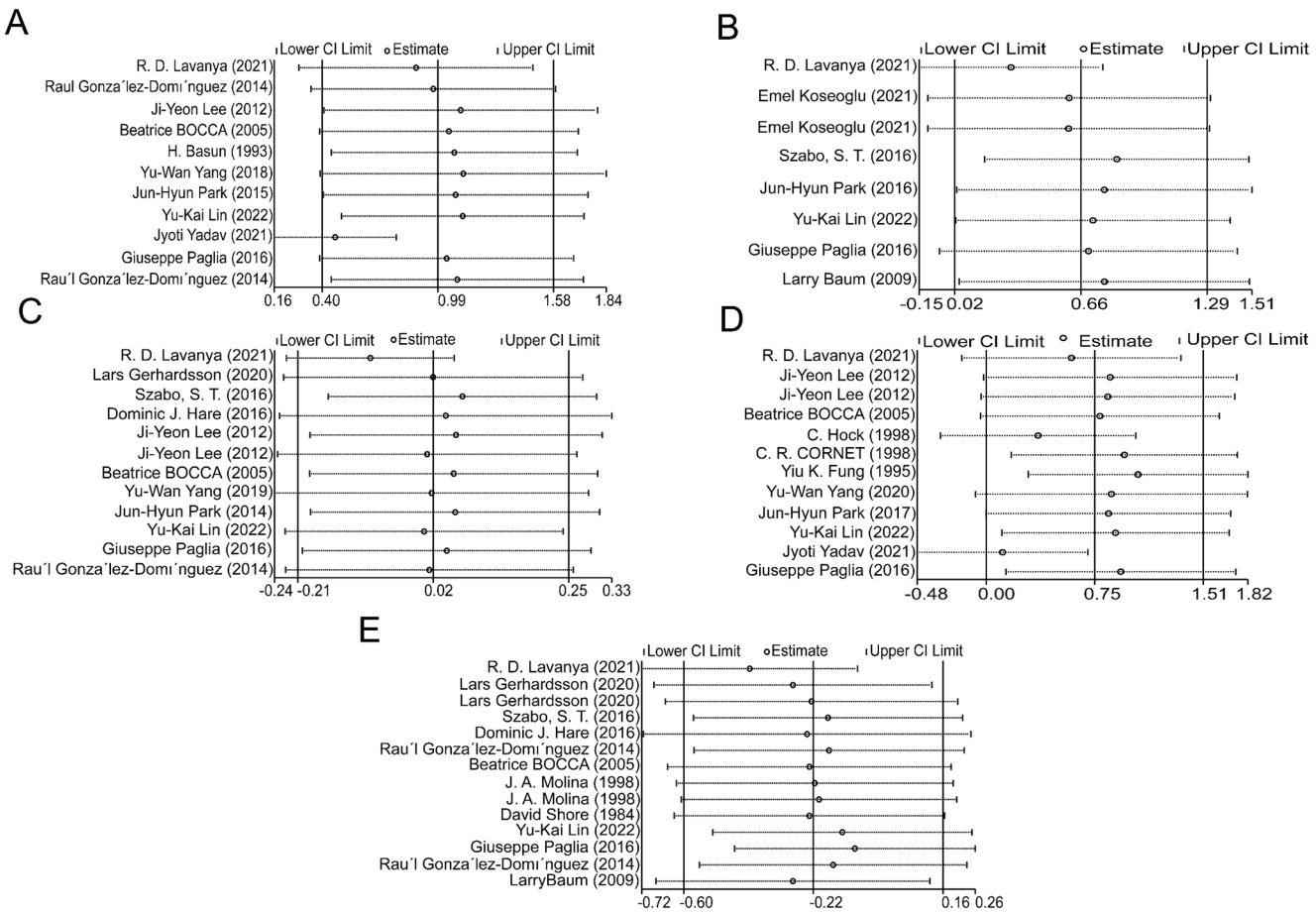

Fig. 3 Sensitivity analysis of correlation between heavy metal content in different biological samples and Alzheimer's Disease. **A** Sensitivity analysis of Cd concentration in AD patients compared with healthy controls. **B** Sensitivity analysis of As concentration in AD patients compared with healthy controls. **C** Sensitivity analysis of Pb concentration in AD patients compared with healthy controls. **D** Sensitivity analysis of Hg concentration in AD patients compared with healthy controls. **E** Sensitivity analysis of Mn concentration in AD patients compared with healthy controls

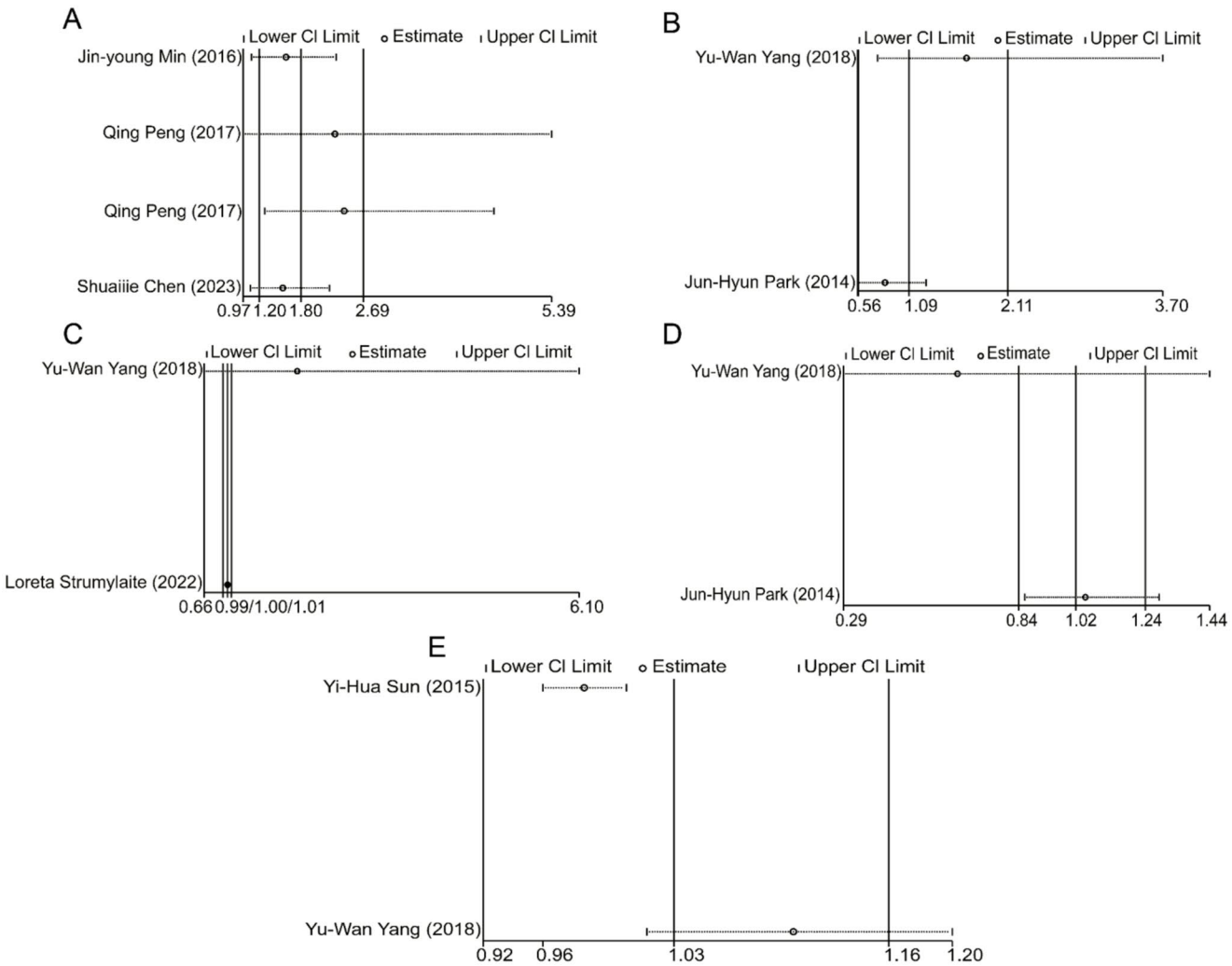

Fig. 4 Sensitivity analysis of correlation between heavy metal exposure and Alzheimer's Disease. **A** Sensitivity analysis of the association between cadmium exposure and Alzheimer's disease mortality. **B** Sensitivity analysis of the association between cadmium exposure and Alzheimer's disease prevalence. **C** Sensitivity analysis of the association between arsenic exposure and Alzheimer's disease prevalence. **D** Sensitivity analysis of the association between lead exposure and Alzheimer's disease prevalence. **E** Sensitivity analysis of the association between mercury exposure and Alzheimer's disease prevalence

et al. 2020; Jiang et al. 2025). Recently, some research has identified a potential relationship between exposure to heavy metal and Alzheimer's disease, though the evidence remains inconclusive (Doroszkiewicz et al. 2023; Korde and Humpel 2024; Olloquequi et al. 2024). The current investigation assessed the effects of five heavy metals on Alzheimer's disease prevalence and mortality.

Our investigation revealed that Cd concentrations in the biological samples of individuals with Alzheimer's disease were higher than those observed in the non-diseased group. This finding aligns with the results of previous studies by Bocca et al. (2005), Park et al. (2014), Babić Leko et al. (2022). However, 2 studies reported no statistical variation in cadmium levels between AD patients and healthy individuals, possibly owing to the restricted number of participants (Basun et al. 1994; Yang et al. 2018). Moreover, a comprehensive analysis of observational studies indicated that individuals with higher cadmium exposure tended to show higher Alzheimer's disease–related mortality. Several studies support our findings (Min and Min 2016; Peng et al. 2017; Chen et al. 2023). Conversely, several research has shown no association between exposure to cadmium and Alzheimer's disease mortality (Park et al. 2014; Yang et al. 2018). The lack of statistical significance in Chen's study may be attributed to its focus on Alzheimer's disease prevalence among individuals with high blood pressure, which may not have been a representative sample. The exact mechanism by which Cd pathogenicity induces AD remains unclear. However, the possible reason shown in animal models is that Cd exposure can increase APP/

PS1A-β plaque deposition and blood-brain barrier permeability, aggravate inflammatory response, and activate microglia. The interaction between APP/PS1 gene and Cd in the surrounding environment can aggravate the advancement of Alzheimer's disease (Liu et al. 2023). Other studies have shown that cortical and hippocampal neurons are the central targets of cadmium-induced neurotoxicity (Shukla et al. 1996). Cd can pass through neurons through voltage-gated calcium channels and initiate apoptosis pathways by provoking stress responses of neurons in the cerebral cortex (López et al. 2003; Gao et al. 2014).

Our research demonstrated elevated arsenic levels in AD group relative to the control group. These findings are corroborated by two other independent studies (Koseoglu et al. 2021; Lavanya et al. 2021). However, several investigations have reported results that were not statistically relevant (Baum et al. 2010; Park et al. 2014; Szabo et al. 2016; Lin et al. 2022). Notably, few previous reviews have highlighted positive associations between arsenic exposure and Alzheimer's disease. While the contribution made by arsenic in the etiology of Alzheimer's disease remains uncertain, with the precise mechanisms yet to be fully explained, some studies suggest that cellular proliferation and oxidative stress, along with alterations in DNA methylation, may play a role (Wei et al. 2024). It has also been proposed that As can elicit an inflammatory response in the brain, which contributes to the formation of tau and ASβ (Giasson et al. 2002). Additionally, research has shown that As disrupts nitric oxide signaling, promotes cell apoptosis, and induces cortical reprogramming through S-nitrosylation, ultimately resulting in neurotoxicity (Tripathi et al. 2022). The conclusions of the subgroup analysis highlighted that the results were significant in the studies conducted in Asia. In a cross-sectional study conducted in China similarly supports our idea, consistent with our findings, Wang et al. identified arsenic poisoning as a contributor to cognitive impairment, which is also an important clinical manifestation of Alzheimer's disease (Wang et al. 2021).

In our meta-analysis of lead, no evident connection was noted between exposure to lead and Alzheimer's disease. Nonetheless, the neurotoxicity of lead is well-documented. Lead can act as a substitute for calcium in various cellular processes, disrupting tight junctions and increasing blood-brain barrier permeability. Additionally, elevated lead concentrations have been linked to DNA methylation and the development of neurodegenerative diseases (Zheng et al. 2003; Jomova and Valko 2011). Exposure to lead has been associated with an expanded susceptibility to adult neurodegenerative disorders, particularly Alzheimer's disease, potentially mediated through various mechanisms such as epigenetic alterations, delayed onset of cardiovascular and renal diseases, direct damage to the central nervous system by mobilizing lead from bone, and diminished neurological and cognitive reserves (Reuben 2018). The relationship between lead and Alzheimer's disease prevalence and mortality still needs further research evidence.

Similarly, in the meta-analysis of mercury and manganese, we did not reveal a meaningful association with Alzheimer's disease. Nevertheless, mercury is believed to influence the pathogenesis of Alzheimer's disease, previous studies have highlighted the neurotoxic effects of mercury (Monnet-Tschudi et al. 2006; Althobaiti 2024). In the subgroup analysis of mercury studies conducted in Asia suggested a possible association, with two studies from India supporting these findings (Chakraborty 2017; Lavanya et al. 2021). This may also be attributed to higher levels of mercury biomarkers observed in Asian populations (Tian and Guo 2023). Major sources of mercury contain human-driven sources, fish intake, natural exposure, and vaccines (Sundseth et al. 2017). Interestingly, some research suggests that the arsenic measurements in the biological samples of individuals with Alzheimer's disease is significantly lower than in non-AD controls (Fung et al. 1995; Cornett et al. 1998; Paglia et al. 2016). Regarding manganese, its involvement in Alzheimer's disease is purported to be linked to the aggregation of alpha-synuclein within cells, leading to synaptic dysfunction and axonal transport impairments (Tyczyńska et al. 2024). However, current evidence remains insufficient to establish a definitive link between manganese and Alzheimer's disease. Therefore, more investigations remain necessary to clarify the link between mercury, manganese, and Alzheimer's disease prevalence and mortality. It is also important to recognize that Alzheimer's disease itself may lead to alterations in metal concentrations, thereby introducing the possibility of reverse causality. Neurodegenerative processes in Alzheimer's disease are characterized by oxidative stress, neuroinflammation, mitochondrial dysfunction, and disruption of the blood–brain barrier, all of which can influence metal metabolism, transport, and redistribution (Sweeney et al. 2018; Haywood 2019; Spotorno et al. 2020). Dysregulation of iron, copper, and zinc homeostasis, for example, has been implicated in amyloid-β aggregation, tau pathology, and neuronal injury (Bush 2003; Ayton et al. 2013; Kim et al. 2018). At the same time, disease-related pathophysiological changes may secondarily affect metal levels in biological matrices (Schrag et al. 2011; Ayton et al. 2013; Li et al. 2017). Consequently, altered metal concentrations observed in patients with Alzheimer's disease—particularly in blood and cerebrospinal fluid—may represent downstream consequences of neurodegeneration rather than primary etiological factors.

Across the included studies, the extent of confounder adjustment varied, which may have contributed to between-study heterogeneity and uncertainty in the pooled estimates.

Nevertheless, most studies adjusted for a core set of key confounders, including age, sex, race/ethnicity, educational attainment, smoking status, and indicators of renal function, with several additionally accounting for socioeconomic status such as household income. This relative consistency in major confounder adjustment improves the comparability of effect estimates.

In the meta-analysis, effect estimates derived from multivariable-adjusted models were used to minimize potential confounding. When multiple models were reported within a study, the estimate from the most fully adjusted model was extracted. However, the specific covariates included in these models varied across studies. Therefore, residual confounding cannot be entirely excluded, and the pooled estimates should be interpreted as average associations across studies with heterogeneous adjustment strategies rather than as definitive causal effects. Our study has the potential to assist in the advancement of strategies with the goal of preventing Alzheimer's disease through the regulation of heavy metal exposure levels. Furthermore, our research serves to enhance public health education. Importantly, our study provides exploratory evidence on the potential associations between five heavy metals and Alzheimer's disease prevalence and mortality, offering preliminary insights into possible risk factors for Alzheimer's disease and informing future research and preventive strategies. To address limitations in previous studies, we expanded upon prior research by including manganese as an additional heavy metal. Furthermore, for all five heavy metals, separate meta-analyses were conducted using standardized mean differences (SMDs) for concentration comparisons and odds ratios or hazard ratios for exposure–outcome associations.

Nevertheless, several limitations should be noted when interpreting our findings. A critical challenge in interpreting our findings is the substantial between-study heterogeneity observed across most pooled analyses, with I^2 values frequently exceeding 90%. Such heterogeneity indicates that the variability in effect estimates cannot be explained by random error alone, and therefore the pooled estimates should not be interpreted as precise or universal effect sizes. Rather, these summary estimates primarily reflect the overall direction and average magnitude of associations across diverse study settings. Although subgroup analyses were performed to examine the differences in concentrations of five heavy metals between AD individuals and healthy controls, the study population in each subgroup was limited, and the presence of residual heterogeneity, therefore, these findings should be interpreted with caution and regarded as hypothesis-generating rather than conclusive. In addition, the included studies differed in the confounders adjusted in their statistical analyses, potentially leading to inconsistent effect estimates, increased residual confounding, and instability in the pooled effect sizes, thereby affecting interpretability and generalizability. Crucially, the reported associations may not solely reflect a causal effect of heavy metal exposure on Alzheimer's disease. Neurodegenerative changes, such as neuronal loss, blood-brain barrier disruption, and altered metal metabolism, could themselves affect metal accumulation or distribution (Haywood 2019; Spotorno et al. 2020; Levi et al. 2024; Chen et al. 2025). Given that several included studies are cross-sectional, the directionality of these associations remains uncertain. Therefore, the observed relationships may reflect a potential bidirectional effect, in which both heavy metal exposure contributes to neurodegeneration and Alzheimer's disease pathology alters metal homeostasis. These limitations underscore the need for well-designed longitudinal studies to clarify causality. Further high-quality studies are needed to validate these findings and provide a more comprehensive assessment of these risk factors.

Conclusion

Our findings contribute to the growing body of observational evidence examining potential associations between heavy metal exposure and Alzheimer's disease. Given the heterogeneity across studies and the predominance of non-prospective designs, these results should be interpreted cautiously. Further well-designed prospective and mechanistic studies are needed to clarify the directionality and potential biological pathways underlying these associations.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12403-026-00769-w.

Acknowledgements The authors express their gratitude to the contributions of all the original study authors.

Author Contributions Guarantor of article: Drs. Chuncheng Lu and Yun Fan. Yaohui Fang: Conceptualization, Data curation, Writing - original draft, Software. Huma Shahzad and Zhi Li: Conceptualization, Data curation, Writing - original draft, Software. Jiarong Zhang, Xinru Wang, Ziyan Qiao, Hong Qian and Qiaoqiao Xu: Writing - review & editing. Yun Fan and Chuncheng Lu: Project administration, Supervision, Validation. All authors reviewed and approved the final version of the manuscript. Yaohui Fang, Huma Shahzad and Zhi Li should be considered joint first authors.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data Availability The data providing evidence for this article will be made obtainable upon appropriate request to the corresponding author.

Declarations

Conflict of interest The authors have no conflict of interest to declare.

Ethical Approval Ethics approval was not required.

References

Althobaiti NA (2024) Heavy metals exposure and Alzheimer's disease: underlying mechanisms and advancing therapeutic approaches. Behav Brain Res 476:115212

Ayton S, Lei P, Bush AI (2013) Metallostasis in Alzheimer's disease. Free Radic Biol Med 62:76–89. https://doi.org/10.1016/j.freeradbiomed.2012.10.558

Babić Leko M, Mihelčić M, Jurasović J et al (2022) Heavy Metals and Essential Metals Are Associated with Cerebrospinal Fluid Biomarkers of Alzheimer's Disease. Int J Mol Sci 24:467. https://doi.org/10.3390/ijms24010467

Basun H, Lind B, Nordberg M et al (1994) Cadmium in blood in Alzheimer's disease and non-demented subjects: results from a population-based study. Biometals. https://doi.org/10.1007/BF00140482

Baum L, Chan IHS, Cheung SK-K et al (2010) Serum zinc is decreased in Alzheimer's disease and serum arsenic correlates positively with cognitive ability. Biometals 23:173–179. https://doi.org/10.1007/s10534-009-9277-5

Bjørklund G, Dadar M, Chirumbolo S et al (2020) Metals, autoimmunity, and neuroendocrinology: Is there a connection? Environ Res 187:109541. https://doi.org/10.1016/j.envres.2020.109541

Bocca B, Forte G, Petrucci F et al (2005) Monitoring of chemical elements and oxidative damage in patients affected by Alzheimer's disease. Ann DellIstituto Super Sanità 41:197–203

Bush AI (2003) The metallobiology of Alzheimer's disease. Trends Neurosci 26:207–214. https://doi.org/10.1016/S0166-2236(03)00067-5

Chakraborty P (2017) Mercury exposure and Alzheimer's disease in India - An imminent threat? Sci Total Environ 589:232–235. https://doi.org/10.1016/j.scitotenv.2017.02.168

Chen S, Shen R, Shen J et al (2023) Association of blood cadmium with all-cause and cause-specific mortality in patients with hypertension. Front Public Health 11:1106732. https://doi.org/10.3389/fpubh.2023.1106732

Chen L, Shen Q, Liu Y et al (2025) Homeostasis and metabolism of iron and other metal ions in neurodegenerative diseases. Signal Transduct Target Ther 10:31. https://doi.org/10.1038/s41392-024-02071-0

Cornett CR, Ehmann WD, Wekstein DR, Markesbery WR (1998) Trace elements in Alzheimer's disease pituitary glands. Biol Trace Elem Res 62:107–114. https://doi.org/10.1007/BF02820026

Dettori JR, Norvell DC, Chapman JR (2022) Fixed-Effect vs Random-Effects Models for Meta-Analysis: 3 Points to Consider. Glob Spine J 12:1624–1626. https://doi.org/10.1177/21925682221110527

Doroszkiewicz J, Farhan JA, Mroczko J et al (2023) Common and Trace Metals in Alzheimer's and Parkinson's Diseases. Int J Mol Sci 24:15721. https://doi.org/10.3390/ijms242115721

Eiró LG, Ferreira MKM, Frazão DR et al (2021) Lead exposure and its association with neurological damage: systematic review and meta-analysis. Environ Sci Pollut Res 28:37001–37015. https://doi.org/10.1007/s11356-021-13536-y

Filippini T, Cilloni S, Malavolti M et al (2018) Dietary intake of cadmium, chromium, copper, manganese, selenium and zinc in a Northern Italy community. J Trace Elem Med Biol 50:508–517. https://doi.org/10.1016/j.jtemb.2018.03.001

Filippini T, Torres D, Lopes C et al (2020) Cadmium exposure and risk of breast cancer: A dose-response meta-analysis of cohort studies. Environ Int 142:105879. https://doi.org/10.1016/j.envint.2020.105879

Fung YK, Meade AG, Rack EP et al (1995) Determination of Blood Mercury Concentrations in Alzheimer's Patients. J Toxicol Clin Toxicol 33:243–247. https://doi.org/10.3109/15563659509017991

Gao S, Cheng Y, Jin Y et al (2014) The relationship between cholesterol and cognitive function is homocysteine-dependent. Clin Interv Aging. https://doi.org/10.2147/CIA.S64766

Giasson BI, Sampathu DM, Wilson CA et al (2002) The Environmental Toxin Arsenite Induces Tau Hyperphosphorylation. Biochemistry 41:15376–15387. https://doi.org/10.1021/bi026813c

González-Domínguez R, García-Barrera T, Gómez-Ariza JL (2014) Homeostasis of metals in the progression of Alzheimer's disease. Biometals 27:539–549. https://doi.org/10.1007/s10534-014-9728-5

Haywood S (2019) Brain–Barrier Regulation, Metal (Cu, Fe) Dyshomeostasis, and Neurodegenerative Disorders in Man and Animals. Inorganics 7:108. https://doi.org/10.3390/inorganics7090108

Jiang H, Zhang S, Lin Y et al (2025) Roles of serum uric acid on the association between arsenic exposure and incident metabolic syndrome in an older Chinese population. J Environ Sci 147:332–341. https://doi.org/10.1016/j.jes.2023.12.005

Jomova K, Valko M (2011) Advances in metal-induced oxidative stress and human disease. Toxicology 283:65–87. https://doi.org/10.1016/j.tox.2011.03.001

Kim AC, Lim S, Kim YK (2018) Metal Ion Effects on Aβ and Tau Aggregation. Int J Mol Sci 19:128. https://doi.org/10.3390/ijms19010128

Korde DS, Humpel C (2024) A combination of heavy metals and intracellular pathway modulators induces Alzheimer disease-like pathologies in organotypic brain slices. Biomolecules 14:165. https://doi.org/10.3390/biom14020165

Koseoglu E, Kutuk B, Nalbantoglu OU et al (2021) Arsenic and selenium measurements in nail and hair show important relationships to Alzheimer's disease in the elderly. J Trace Elem Med Biol 64:126684. https://doi.org/10.1016/j.jtemb.2020.126684

Lavanya RD, Reddy BS, Abdul Sattar S, Rao ADP (2021) Trace element imbalances in blood serum of Alzheimer's disease patients. Spectrosc Lett 54:458–471. https://doi.org/10.1080/00387010.2021.1941124

Levi S, Ripamonti M, Moro AS, Cozzi A (2024) Iron imbalance in neurodegeneration. Mol Psychiatry 29:1139–1152. https://doi.org/10.1038/s41380-023-02399-z

Li D-D, Zhang W, Wang Z-Y, Zhao P (2017) Serum Copper, Zinc, and Iron Levels in Patients with Alzheimer's Disease: A Meta-Analysis of Case-Control Studies. Front Aging Neurosci 9:300. https://doi.org/10.3389/fnagi.2017.00300

Lin Y-K, Liang C-S, Tsai C-K et al (2022) A Metallomic Approach to Assess Associations of Plasma Metal Levels with Amnestic Mild Cognitive Impairment and Alzheimer's Disease: An Exploratory Study. J Clin Med 11:3655. https://doi.org/10.3390/jcm11133655

Liu J, Xie Y, Lu Y et al (2023) APP/PS1 Gene-Environmental Cadmium Interaction Aggravates the Progression of Alzheimer's Disease in Mice via the Blood-Brain Barrier, Amyloid-β, and Inflammation. J Alzheimers Dis 94:115–136. https://doi.org/10.3233/JAD-221205

Livingston G, Huntley J, Sommerlad A et al (2020) Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 396:413–446. https://doi.org/10.1016/S0140-6736(20)30367-6

López E, Figueroa S, Oset-Gasque MJ, González MP (2003) Apoptosis and necrosis: two distinct events induced by cadmium in cortical neurons in culture. Br J Pharmacol 138:901–911. https://doi.org/10.1038/sj.bjp.0705111

Min J, Min K (2016) Blood cadmium levels and Alzheimer's disease mortality risk in older US adults. Environ Health 15:69. https://doi.org/10.1186/s12940-016-0155-7

Monastero RN, Vacchi-Suzzi C, Marsit C et al (2018) Expression of Genes Involved in Stress, Toxicity, Inflammation, and Autoimmunity in Relation to Cadmium, Mercury, and Lead in Human Blood: A Pilot Study. Toxics 6:35. https://doi.org/10.3390/toxics6030035

Monnet-Tschudi F, Zurich M-G, Boschat C et al (2006) Involvement of environmental mercury and lead in the etiology of neurodegenerative diseases. Rev Environ Health. https://doi.org/10.1515/REVEH.2006.21.2.105

Nichols E, Steinmetz JD, Vollset SE et al (2022) Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. Lancet Public Health 7:e105–e125. https://doi.org/10.1016/S2468-2667(21)00249-8

Obeng-Gyasi E (2019) Sources of lead exposure in various countries. Rev Environ Health 34:25–34. https://doi.org/10.1515/reveh-2018-0037

Ohsawa M (2009) Heavy Metal-induced Immunotoxicity and Its Mechanisms. Yakugaku Zasshi 129:305–319. https://doi.org/10.1248/yakushi.129.305

Olloquequi J, Díaz-Peña R, Verdaguer E et al (2024) From Inhalation to Neurodegeneration: Air Pollution as a Modifiable Risk Factor for Alzheimer's Disease. Int J Mol Sci 25:6928. https://doi.org/10.3390/ijms25136928

World Health Organization (2021) Global status report on the public health response to dementia

Paduraru E, Iacob D, Rarinca V et al (2022) Comprehensive Review Regarding Mercury Poisoning and Its Complex Involvement in Alzheimer's Disease. Int J Mol Sci 23:1992. https://doi.org/10.3390/ijms23041992

Paglia G, Miedico O, Cristofano A et al (2016) Distinctive Pattern of Serum Elements During the Progression of Alzheimer's Disease. Sci Rep 6:22769. https://doi.org/10.1038/srep22769

Park J-H, Lee D-W, Park KS, Joung H (2014) Serum Trace Metal Levels in Alzheimer's Disease and Normal Control Groups. Am J Alzheimers Dis Dementias® 29:76–83. https://doi.org/10.1177/1533317513506778

Peng Q, Bakulski KM, Nan B, Park SK (2017) Cadmium and Alzheimer's disease mortality in U.S. adults: Updated evidence with a urinary biomarker and extended follow-up time. Environ Res 157:44–51. https://doi.org/10.1016/j.envres.2017.05.011

Qiu C, Kivipelto M, Von Strauss E (2009) Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. Dialogues Clin Neurosci 11:111–128. https://doi.org/10.31887/DCNS.2009.11.2/cqiu

Racette BA, Nelson G, Dlamini WW et al (2021) Severity of parkinsonism associated with environmental manganese exposure. Environ Health 20:27. https://doi.org/10.1186/s12940-021-00712-3

Rahmani A, Khamutian S, Doosti-Irani A et al (2023) The association of arsenic exposure with mortality due to cancer, diabetes, Alzheimer's and congenital anomalies using Poisson regression. Sci Rep 13:15456. https://doi.org/10.1038/s41598-023-42744-4

Reitz C, Brayne C, Mayeux R (2011) Epidemiology of Alzheimer disease. Nat Rev Neurol 7:137–152. https://doi.org/10.1038/nrneurol.2011.2

Reuben A (2018) Childhood Lead Exposure and Adult Neurodegenerative Disease. J Alzheimers Dis 64:17–42. https://doi.org/10.3233/JAD-180267

Scheltens P, Blennow K, Breteler MMB et al (2016) Alzheimer's disease. Lancet 388:505–517. https://doi.org/10.1016/S0140-6736(15)01124-1

Schrag M, Crofton A, Zabel M et al (2011) Effect of Cerebral Amyloid Angiopathy on Brain Iron, Copper, and Zinc in Alzheimer's Disease. J Alzheimers Dis JAD 24:137–149. https://doi.org/10.3233/JAD-2010-101503

Shukla A, Shukla GS, Srimal R (1996) Cadmium-induced alterations in blood- brain barrier permeability and its possible correlation with decreased microvessel antioxidant potential in rat. Hum Exp Toxicol 15:400–405. https://doi.org/10.1177/096032719601500507

Spotorno N, Acosta-Cabronero J, Stomrud E et al (2020) Relationship between cortical iron and tau aggregation in Alzheimer's disease. Brain 143:1341–1349. https://doi.org/10.1093/brain/awaa089

Sundseth K, Pacyna J, Pacyna E et al (2017) Global Sources and Pathways of Mercury in the Context of Human Health. Int J Environ Res Public Health 14:105. https://doi.org/10.3390/ijerph14010105

Sweeney MD, Sagare AP, Zlokovic BV (2018) Blood–brain barrier breakdown in Alzheimer's disease and other neurodegenerative disorders. Nat Rev Neurol 14:133–150. https://doi.org/10.1038/nrneurol.2017.188

Szabo ST, Harry GJ, Hayden KM et al (2016) Comparison of Metal Levels between Postmortem Brain and Ventricular Fluid in Alzheimer's Disease and Nondemented Elderly Controls. Toxicol Sci 150:292–300. https://doi.org/10.1093/toxsci/kfv325

Tian K, Guo D (2023) Comparison of the accumulation of toxic metal biomarkers in Asian subgroups and other races in the United States: NHANES 2015–2016. Chemosphere 336:139319

Tripathi MK, Kartawy M, Ginzburg S, Amal H (2022) Arsenic alters nitric oxide signaling similar to autism spectrum disorder and Alzheimer's disease-associated mutations. Transl Psychiatry 12:127. https://doi.org/10.1038/s41398-022-01890-5

Tyczyńska M, Gędek M, Brachet A et al (2024) Trace Elements in Alzheimer's Disease and Dementia: The Current State of Knowledge. J Clin Med 13:2381. https://doi.org/10.3390/jcm13082381

Wang M, Hossain F, Sulaiman R, Ren X (2019) Exposure to Inorganic Arsenic and Lead and Autism Spectrum Disorder in Children: A Systematic Review and Meta-Analysis. Chem Res Toxicol 32:1904–1919. https://doi.org/10.1021/acs.chemrestox.9b00134

Wang X, Huang X, Zhou L et al (2021) Association of arsenic exposure and cognitive impairment: A population-based cross-sectional study in China. Neurotoxicology 82:100–107. https://doi.org/10.1016/j.neuro.2020.11.009

Wei Y, Zhou Y, Xiao L et al (2024) Associations of Heavy Metals with Cognitive Function: An Epigenome-Wide View of DNA Methylation and Mediation Analysis. Ann Neurol 96:87–98. https://doi.org/10.1002/ana.26942

Yang Y-W, Liou S-H, Hsueh Y-M et al (2018) Risk of Alzheimer's disease with metal concentrations in whole blood and urine: A case–control study using propensity score matching. Toxicol Appl Pharmacol 356:8–14. https://doi.org/10.1016/j.taap.2018.07.015

Yslas AR, Park R, Nishimura N, Lee E (2024) Monomeric and oligomeric amyloid-β cause distinct Alzheimer's disease pathophysiological characteristics in astrocytes in human glymphatics-on-chip models. Lab Chip 24:3826–3839. https://doi.org/10.1039/D4LC00287C

Zhang X, Wang J, Zhang Z, Ye K (2024) Tau in neurodegenerative diseases: molecular mechanisms, biomarkers, and therapeutic strategies. Transl Neurodegener 13:40. https://doi.org/10.1186/s40035-024-00429-6

Zheng W, Aschner M, Ghersi-Egea J-F (2003) Brain barrier systems: a new frontier in metal neurotoxicological research. Toxicol Appl Pharmacol 192:1–11. https://doi.org/10.1016/S0041-008X(03)00251-5