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REVIEW

Alzheimer's Disease and Circulatory Imbalance of Toxic Heavy Metals: A Systematic Review and Meta-analysis of Clinical Studies

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Abstract

The role of heavy metals on human health has often been discussed regarding disease pathogenesis and risk factors. Alzheimer's disease (AD), a prevalent neurodegenerative disease, is no exception. We conducted a comprehensive examination to assess the concentrations of lead (Pb), cadmium (Cd), arsenic (As), and mercury (Hg) in biological samples of AD patients in comparison with a group of individuals without AD, with the objective of our study being to perform a systematic review on this topic. We performed this systematic review by searching various databases/search engines, including Web of Science, Scopus, PubMed, and Google Scholar, until December 7, 2022. Relevant studies were scrutinized for eligibility. Meta-analysis was performed on studies with sufficient data using STATA software. Twenty-seven out of 3349 studies met pre-defined eligibility criteria and were included in our systematic review. For the meta-analysis, 22 studies with 3346 participants (1291 AD patients and 2055 healthy controls) had sufficient data for inclusion in the analysis. Using a random-effects model, we found that pooled data indicated patients with AD had significantly higher levels of Cd in their biological samples compared to controls (Hedges' g, 0.83; 95% CI, 0.11, 1.54; $p = 0.023$). However, other heavy metals were not significantly different in circulatory samples of AD patients compared to healthy controls ($p > 0.05$). This systematic review and meta-analysis indicated that Cd concentrations in AD patients were significantly higher than in healthy controls. Other included heavy metals may not be directly associated with increased risk of AD.

Keywords Alzheimer's disease · Cadmium · Lead · Mercury · Arsenic · Heavy metals · Toxic metals · Dementia

Introduction

Alzheimer's disease (AD) is recognized as a global priority by the World Health Organization (WHO). AD is a prevalent neurodegenerative condition that results in cognitive impairment and memory loss, making it the leading cause of dementia [1, 2]. More than 46 million people are diagnosed with dementia worldwide, with approximately 70% of cases involving AD [3–5].

Although several pathological mechanisms have been proposed for AD, two hallmark pathologies involve amyloid-beta peptide (Aβ) formation and tau protein aggregation, causing extracellular plaque deposition and neurofibrillary tangle formations in the brain, respectively [3]. Despite the high prevalence of AD, there is no established treatment [1]. Therefore, characterizing risk factors and prevention is prudent.

The risk of AD is mainly attributed to genetic and environmental factors [5]. Due to the ongoing expansion

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of industry in developing countries, which results in the emission of toxic airborne chemicals, heavy metal exposures are more commonly reported. Heavy metals are contributors and risk factors in many diseases [5]. For instance, cadmium (Cd) and lead (Pb) are notable for their association with neurotoxicity [5, 6]. Electronic wastes, inexpensive jewelry, and toys are common sources of Cd [6].

In contrast, lead sources include lead-based paints and solders, bullets, ceramics, industrial emissions, contaminated food, water, soil, and alternative health supplements [7]. Arsenic (As) is associated with peripheral neuropathy and oxidative DNA damage [6]. According to the WHO, human exposure to As is primarily due to groundwater consumption and crop irrigation from said water source [6]. Mercury (Hg) exposure in humans can occur via natural and anthropogenic sources such as volcanic eruption, gold mining activities, chemical wastes, and consumption of contaminated seafood and induce AD by Aβ formation via oxidative stress [8, 9]. These toxic metals cross the blood–brain barrier (BBB), with evidence suggesting a link between Aβ formation, tau accumulation, and oxidative stress, leading to apoptosis in neural cells [5]. These metals traverse the BBB with passive diffusion and facilitated transport processes. Pb can easily cross the BBB due to its structural similarity to calcium, allowing it to mimic calcium-dependent transport systems [10] as it enters the tissue using aquaporin channels and sodium-coupled nutrient transporters [11]. Hg can pass through the BBB as the organic and inorganic forms, with the organic methylmercury being more lipophilic and readily crossing the barrier [12]. Lastly, Cd disrupts the integrity of the BBB and enters the brain through divalent metal transporters and calcium channels [13].

A previous meta-analysis study on a similar matter has shown that the level of Pb is significantly lower in AD patients, which cannot be justified due to the toxic effect of Pb on the neurological system [4]. Additionally, it has been stated that Cd and Hg are significantly higher in AD patients compared to controls, however, more related studies require analyses with subgrouping to better contextualize these results [4]. The method used to measure toxic metals and the countries where these studies were conducted can increase heterogeneity and influence the results.

Identifying environmental risk factors of AD may advance and inform a more comprehensive understanding of the disease pathology, which may impact treatment and prevention. Consequently, due to the limited literature reviews on this subject matter, our objective was to conduct a systematic review and meta-analysis to evaluate the concentrations of the four relevant toxic heavy metals (Hg, Pb, Cd, As) in biological samples of AD patients compared to healthy controls.

Methods

Study Design and Literature Search

This systematic review and meta-analysis have been carried out according to PRISMA guidelines. Three independent individuals (AK, RF, and SK) performed an extensive database search until December 7, 2022, utilizing both keywords and MESH terms. There was no date limit, and all studies were included from the earliest time available. We conducted searches in four databases/search engines, namely Web of Science, Scopus, PubMed, and Google Scholar, using MESH terms and keywords. The searches were performed on the title or abstract of the studies. The search strategies employed in all four databases are detailed in Table 1. The records of different databases were exported and managed using Mendeley software. We also added our systematic review to PROSPERO registration with ID CRD558007.

Eligibility Criteria

Inclusion Criteria

Studies that investigated human blood or cerebrospinal fluid (CSF) concentrations for at least one of the heavy metals of interest were included. Studies with two groups of AD patients and controls were considered. Since studies are mainly performed in adults due to AD, we did not consider an age limit for the systematic review and meta-analysis. No limitations on language and time of studies were imposed, and articles in English language or at least one English abstract were included. The references of relevant studies were also assessed for additional related documents. Studies that reported mean and standard deviation for the concentration of the metals in two groups of AD patients and healthy controls were included. The results of relevant articles with insufficient data (did not have any numerical form of report for the concentrations of metals that can be analyzed) for meta-analysis were only reported in our systematic review section. In all the studies, the control groups were age- and gender-matched with the AD group. Further, controls were healthy and had not been diagnosed with AD or another neurodegenerative disease.

Exclusion Criteria

Review studies, books, letters to the editor, and experimental studies were not included. Irrelevant studies that did not report outcomes of interest were also excluded in the different stages of document screening. First, the total records of the databases were pooled and the duplicates were deleted.

Table 1 Search strategies are employed across different databases to retrieve the desired and applicable documents

Database/search engine	Search strategy	Results
Pub Med	((((((((((((((((((("toxic metal"[Title/Abstract]) OR ("heavy metal"[Title/Abstract])) OR (cadmium[Title/Abstract])) OR (arsenic[Title/Abstract])) OR (mercury[Title/Abstract])) OR (arsenic[MeSH Terms])) OR (cadmium[MeSH Terms])) OR (mercury[MeSH Terms])) OR (lead[MeSH Terms])) OR (trace metal[Title/Abstract])) OR ("heavy metals"[Title/Abstract])) OR ("toxic metals"[Title/Abstract])) OR (cd[Title/Abstract])) OR (hg[Title/Abstract])) OR (pb[Title/Abstract])) AND ((((((("Alzheimer's disease"[Title/Abstract]) OR (Alzheimer's[Title/Abstract])) OR (Alzheimer[Title/Abstract])) OR ("Neurocognitive disorders"[Title/Abstract])) OR ("Neurocognitive disorder"[Title/Abstract])) OR ("Alzheimer Disease"[MeSH Terms] OR (Dementia[Title/Abstract])) OR (Dementia[MeSH Terms]))))))	1854
Scopus	(TITLE-ABS("Alzheimer's disease" OR Alzheimer's OR Dementia OR Alzheimer)) AND ((CHEMNAME(lead)) OR (TITLE-ABS(arsenic OR mercury OR cadmium OR "heavy metal" OR "toxic metal" OR hg OR cd OR pb OR "heavy metals" OR "toxic metals" OR "trace metal")))	2073
Web of Science	ti = ((Alzheimer OR Alzheimer's OR Dementia) AND ("heavy metals" OR "heavy metal" OR "toxic metal" OR "toxic metals" OR "arsenic" OR mercury OR cadmium OR lead OR cd OR hg OR pb))	541
	ab = ((Alzheimer OR Alzheimer's OR Dementia)) AND (ti = (lead) OR ab = ("heavy metals" OR "heavy metal" OR "toxic metal" OR "toxic metals" OR "arsenic" OR mercury OR cadmium OR pb OR hg OR cd))	2190
Google Scholar	allintitle:(Alzheimer OR Alzheimer's OR dementia)("heavy metal" OR "heavy metals" OR "toxic metal" OR "toxic metals" OR "trace metal" OR Arsenic OR cadmium OR mercury OR lead OR cd OR pb OR hg)	741

Next, the studies that did not meet our inclusion criteria were excluded after a review of their titles and abstracts. The remaining studies that were deemed relevant underwent a full-text examination.

A third author (AK) resolved the discrepancies between the reviewers regarding article inclusion.

Data Extraction

Information from related studies is obtained and presented in Table 2. An electronic data abstraction form was used for recording study characteristics, such as the name of the first author, year, country, type of study, diagnostic criteria for AD, sample size, mean age of participants, biological sex, assessment method for different metals in circulatory samples, type of body fluid, and the main results of the study. For studies in the full text that have yet to be found, we included them if the data were enough for analysis and inclusion in the systematic review by abstract. If full text was unavailable, we emailed the authors and did our best to find any relevant data's full text. Therefore, we have included more studies than other similar studies, which can make our findings more precise.

Quality Assessment

A pre-defined checklist was used to appraise the quality of the included studies. Each study was evaluated by two reviewers using the Joanna Briggs Institute (JBI) critical assessment tool. The discrepancy was rechecked by a third researcher (SN). The JBI tool consists of questions that must be answered with "yes" or "no." If the answer is "yes," it earns one point, while a "no" or unclear answer earns zero points [14]. No studies that met our research criteria were excluded from the quality evaluation stage.

Meta-Analysis

The meta-analysis was conducted using STATA software (V.17). The *I*-squared (I^2) and chi-square–based *Q*-test assessed heterogeneity in the included studies. If a considerable heterogeneity (I^2 statistic more than 70% and *p*-value of *Q*-test < 0.1) was observed, we analyzed the pooled estimates with a random-effects model. The publication bias was examined using Egger's regression and Begg's rank correlation tests. The statistical analysis was conducted using Hedge's *g* to calculate the effect sizes for the primary outcome measures. Hedge's *g* was chosen to provide an unbiased estimate of the effect size, accounting for potential differences in sample sizes between conditions.

Effect size estimates and their 95% confidence intervals are reported to indicate the magnitude of treatment effects.

Most studies used µg/dl as the unit; the data for other units has been converted to µg/dl. Most studies reported data with mean and standard deviation (SD). Some used the median ± interquartile range, which has been converted into mean and SD. No study was excluded in this section unless the data were incomplete.

Subgroup analysis has been done to reduce possible heterogeneity and increase our knowledge about the findings. We used the human development index (HDI), body fluids, and measurement method for subgrouping, as these results were available in most studies. Studies that did not mention this information were titled as not mentioned (NM) in the analysis.

Table 2 Characteristics included human studies for assessment of toxic metals concentrations in biological samples of Alzheimer's disease compared to healthy individuals

The first author (year)	Country	Type of study	Diagnostic criteria for AD	Sample size control, case	Mean age control, case	Gender F/M control, case	HM assessment method	Body fluid	Main results
Gerhardsson L (2008) [15]	Sweden	Case–control	Clinical diagnosis	54, 173	73 (60–94), 75 (52–86)	36/18, 122/51	ICP-MS	CSF	Cd =
									Hg =
									Pb −
								Plasma	Cd =
									Hg +
									Pb =
Lavanya R D (2021) [16]	India	Case–control	NM	18, 30	NM, 60.29 ± 10.40 (matched)	NM	ICP-MS	Serum	Cd +
									Hg +
									Pb +
									As +
Hock C (1997) [22]	Germany	Case–control	NINCDS-ADRDA criteria	65, 33	36.1, 70.7 ± 11.3	NM, 18/15	AAS	Whole blood	Hg +
Basun H (1991) [27]	Sweden	Case–control	NA	28, 24	NA	NA	NA	CSF	Hg =
									Cd −
									Pb =
								Plasma	Hg +
									Cd +
									Pb =
									As =
Basun H (1994) [28]	Sweden	Case–control	MMSE	17, 5	82 ± 5, 85 ± 3	12/7, 5/1	GAAS	Whole blood	Cd =
Gonzalez-Domınguez R (2014) [17]	Spain	Case–control	NINCDS-ADRDA	30, 30	75.9 ± 5.5, 81.4 ± 4.6	17/13, 18/12	ICP-MS	Serum	Cd =
									Pb =
Hare D J (2016) [18]	Australia	Case–control	NINCDS-ADRDA	758, 206	70.0 ± 7.0, 78.0 ± 8.6	236/222, 127/79	ICP-MS	Serum	Pb =
Guan C (2016) [19]	China	Case–control	NINCD-SADRDA	161, 92	77.84 ± 8.79, 76.59 ± 7.31	90/71, 58/34	ICP-MS	Plasma	Cd =
									Pb =
Alimonti A (2006) [29]	Italy	Case–control	NINCDS-ADRDA	124, 53	44.8 ± 12.7, 74.5 ± 6.5	43/81, 36/17	AES	Serum	Cd =
									Hg =
									Pb =
Baum L (2009) [20]	China	Case–control	NINCDS-ADRDA	41, 44	79.1 ± 6.0, 74.3 ± 8.7	20/21, 29/15	ICP-MS	Serum	As =
Giacoppo S (2014) [21]	Italy	Case–control	NINCDS-ADRDA	10, 15	72.40 ± 8.796, 73.27 ± 10.05	7/3, 4/11	ICP-MS	Whole blood	Hg =
									Pb −
Paglia G (2016) [30]	South Korea	Case–control	NINCDS-ADRDA	40, 34	65.53 ± 6.37, 72.44 ± 7.48	25/15, 25/9	ICP-MS	Serum	Hg −
									Pb =
									As =
									Cd =
Lee J (2012) [31]	South Korea	Case–control	Clinical diagnosis	130, 80	NM	NM	ICP-MS, DMA-80	Serum	Hg =
									Pb =
									Cd =
								Whole blood	Hg =
									Pb −
									Cd =

Table 2 (continued)

The first author (year)	Country	Type of study	Diagnostic criteria for AD	Sample size control, case	Mean age control, case	Gender F/M control, case	HM assessment method	Body fluid	Main results
Lafta H (2021) [23]	Iraq	Case–control	Clinical diagnosis	30, 42	37–75 years, 50–95 years	NM	AAS	Serum	Hg +
									Pb +
									Cd +
Omotosho I (2020) [24]	Sub-Sahara Africa	Case–control	NINCDS-ADRDA	20, 18	Aged ≥ 60 years, age-matched	NM	AAS	Whole blood	Cd +
									Pb +
Fathabadi B (2018) [25]	Iran	Case–control	NIA-AA	54, 27	67.55 ± 6.54, 70.85 ± 8.54	24/30, 12/15	AAS	Serum	Pb +
Park J H (2014) [32]	South Korea	Case–control	NINCDS-ADRDA	67, 64	73.36 ± 5.29, 74.97 ± 5.37	37/30, 34/30	ICP-MS, DMA-80	Serum	Pb =
									Hg =
									Cd =
									As =
Fung Y (1995) [40]	USA	Case–control	NINCDS-ADRDA	9, 9	NM	NM	RNAA	Whole blood	Hg =
Bocca B (2005) [33]	Italy	Case–control	NINCDS-ADRDA, MMSE	44, 60	Older than 45, 74.6 ± 6.39	11/33, 40/20	ICP-AES	Serum	Hg +
									Pb =
									Cd +
								Whole blood	Hg −
									Pb =
									Cd =
Arslan A (2016) [26]	Turkey	Case–control	NINCDS-ADRDA, MMSE	15, 24	70.46 ± 5.237, 75.36 ± 4.124	5/10, 4/20	AAS	Serum	Cd +
									Pb +
Cho J (2017) [41]	South Korea	Case–control	Clinically	216, 108	60–69 or ≥ 70-year-old, NM	NM	NM	Whole blood	Hg =
Zhang S (2010) [38]	China	Case–control	MMSE	20, 50	NM	NM	NM	Plasma	Hg =
									Pb +
Xin-ni L (2012) [39]	China	Case–control	NM	18, 40	NM	NM	ICP-MS	Serum	Pb =
								CSF	Pb =
Gerhardsson L (2011) [34]	Sweden	Case–control	NINCDS-ADRDA	54, 264	73 (60–94), 76 (52–87)	36/18, 179/85	ICP-MS	CSF	Hg −
									Pb −
									Cd =
Yadav J (2021) [35]	India	Case–control	NINCDS-ADRDA	50, 50	74.13, age-matched	NM, 32/18	ICP-OES	Whole blood	Pb ND
									As ND
									Hg +
									Cd +
Yang Y (2018) [36]	Taiwan	Case–control	DMS-IV	264, 170	74.84, 74.99	NM	ICP-MS, Mercury analyzer	Whole blood	Pb =
									Cd =
									Hg =
Lin Y (2022) [37]	Taiwan	Cross-sectional	NIA-AA, MMSE, CDR	9, 8	67, 82.9	6/3, 6/2	ICP-MS	Plasma	As =
									Cd =
									Hg =
									Pb =

F/M, female/male; *AD*, Alzheimer's disease; *NM*, not mentioned; *NA*, not available; *ND*, not detectable; *HM*, heavy metal; *AAS*, atomic absorption spectrometry; *GAAS*, graphite atomic absorption spectrometry; *CSF*, cerebrospinal fluid; *ICP*, individually coupled plasma; *ICP-MS*, individually coupled plasma mass spectrometry; *ICP-AES*, inductively coupled plasma atomic emission spectrometer; −, +, =, respectively indicate the significantly lower, higher, and same level of that element in samples of AD patients compared to controls; *RNNA*, radiochemical neutron activation analysis; *NINCDS-ADRDA*, National Institute of Neurological and Communicative Disorders-Alzheimer's Disease And Related Disorders Association; *MMSE*, The mini-mental state examination; *ICP-OES*, inductively coupled plasma optical emission spectroscopy; *DMS-IV*, Diagnostic and Statistical Manual Fourth Edition criteria

To investigate the effects of age and gender on our outcomes, we employed a meta-regression analysis.

Results

Study Characteristics

Various databases/search engines yielded 7399 studies. Three thousand eight hundred fifty-four articles were deleted as duplicates using Mendeley software. Afterward, we examined the remaining research papers and eliminated 3286 because they were either duplicates, reviews, letters, or books, or did not match our inclusion criteria. Subsequently, we assessed the complete content of the remaining studies and removed 232 of them. Ultimately, 27 studies met the study inclusion criteria for the quality assessment and systematic review (Fig. 1).

The included studies measured at least one of the four heavy metals of interest (Pb, As, Cd, Hg) in patients with AD and healthy controls' serum, plasma, or CSF. Among 27 studies, 22 had sufficient data to be analyzed and were included in the meta-analysis. The publication dates for the included studies span from 1991 to 2022. The concentrations of the heavy metals were assessed using different methods, primarily using inductively coupled plasma (ICP) [15–21] or atomic absorption spectroscopy (AAS) [22–26]. Most studies used NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders-Alzheimer's Disease and Related Disorders Association) criteria for diagnosis of AD [15–26]. The results are shown in Table 2.

Systematic Review and *Meta*-analysis

Cadmium (Cd)

Eighteen studies measured Cd concentrations in different body fluids, including CSF and blood, in AD patients and controls [15–17, 19, 23, 24, 26–37].

Three studies measured CSF concentrations of Cd [15, 27, 34]. Two reported non-significant results [15, 34], while the other reported lower Cd concentrations of CSF in AD patients compared to the controls [27].

Six studies measured Cd in whole blood [24, 28, 31, 33, 35, 36]. Four reported non-significant results [28, 31, 33, 36], while two reported higher Cd concentrations in the whole blood of AD patients compared to controls [24, 35].

Nine studies measured serum Cd concentrations [16, 17, 23, 26, 29–33]. Five studies reported non-significant results

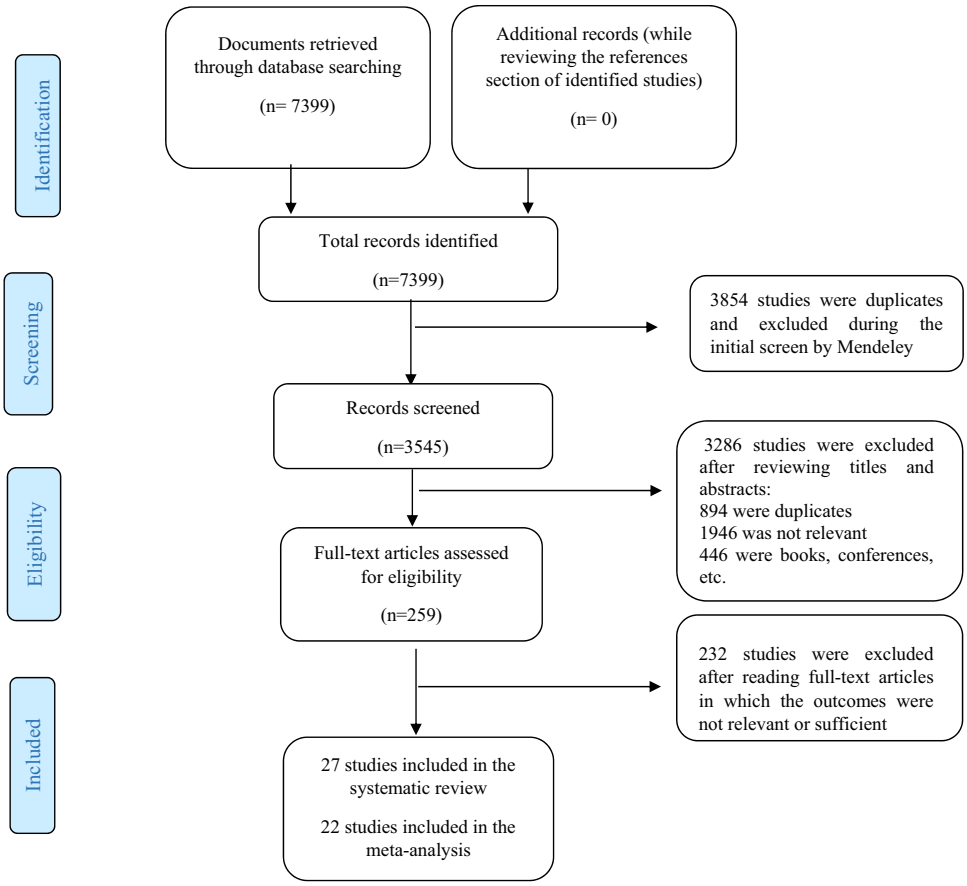


Fig. 1 The PRISMA flowchart illustrates searching the literature and selecting documents according to a predetermined strategy

[17, 29–32], while four others reported higher Cd concentrations in the serum of AD patients [16, 23, 26, 33].

Four studies measured the plasma concentrations of Cd [15, 19, 27, 37]. Three reported a non-significant difference in plasma concentrations of Cd in AD patients compared to controls [15, 19, 37], and one reported higher concentrations in patients with AD [27].

Also, for the meta-analysis, the random effect model pooled Cd concentrations in 618 AD patient samples compared to 819 healthy controls (12 studies). The results showed that Cd concentrations in AD patients were significantly higher than in controls (Hedges' g, 0.80; 95% CI, 0.16, 1.45; $p=0.014$) (Fig. 2). The pooled studies were heterogeneous ($I^2=97.04\%$, $Q=112.48$, $p<0.001$).

The Egger's regression test suggested the presence of a publication bias (z = 3.69, $p=0.0002$).

The results of subgroup analysis based on different samples showed that pooled concentrations of Cd in serum were significantly higher in AD patients than in controls (Hedges' g, 1.22; 95% CI, 0.01, 2.42; $p=0.047$). Additionally, the subgroup analysis based on the assessment method showed that Cd concentrations had significant differences in the ICP method (Hedges' g, 0.50; 95% CI, 0.16, 0.83; $p=0.004$) but not in the AAS method. Results in both developing and developed countries in human development index (HDI) subgrouping showed significantly higher Cd concentrations in AD patients compared to controls (respectively; Hedges' g, 2.25; 95% CI, 0.54, 3.96; $p=0.010$; Hedges' g, 0.26; 95% CI, 0.07, 0.44; $p=0.006$).

The results of meta-regression analyses revealed that continuous factors such as age ($\beta=0.25$, $p=0.01$) were positively related to Cd concentrations, but gender (female) ($\beta=-0.20$, $p=0.002$) was negatively associated with Cd concentrations.

Arsenic (As)

Seven studies measured As concentrations in various body fluids in AD patients versus healthy controls [16, 20, 27, 30, 32, 35, 37]. Two studies measured As concentrations in the plasma [27, 37]. Four studies measured As in the serum of AD patients and controls [16, 20, 30, 32].

All the studies found no statistically significant differences in As concentrations in AD patients compared to controls. However, one study measured As serum concentrations and found higher concentrations in AD patients than in healthy controls [16]. The study that measured As concentrations in whole blood reported that As was undetected [35].

As for the meta-analysis, five studies compared blood As concentrationss of 180 AD patients with 175 controls. This analysis showed a non-significant difference in As concentrations in AD patients' blood compared to healthy controls (Hedges' g, 0.77; 95% CI, −0.57, 2.11; $p=0.260$) (Fig. 3). Heterogeneity was found in the pooled studies ($I^2=97.02\%$, $Q=56.55$, $p<0.001$). The Begg's rank correlation test suggested no publication bias ($z=1.71$, $p=0.0864$). Furthermore, meta-regression analyses explained that age ($\beta=0.02$, $p=0.40$) and gender (female) ($\beta=0.006$, $p=0.76$) had no statistically significant impact on As concentrations.

Lead (Pb)

Twenty-two studies measured Pb concentrations in different body fluids, including CSF and blood, in AD patients and controls [15–19, 21, 23–27, 29–39].

Four studies measured Pb concentrations in CSF [14, 30, 34, 38]. Two reported significantly lower Pb concentrations in AD patients [15, 34] and two reported a non-significant difference compared to controls [34, 38].

Six studies measured Pb concentrations in whole blood [21, 24, 31, 33, 35, 36]. Two documents reported lower Pb concentrations [21, 31], two reported no significant difference [33, 36], one reported higher Pb concentrations [24], and one reported Pb as undetectable in AD patients' whole blood compared to controls [35].

Twelve studies measured Pb serum concentrations [16–18, 23, 25, 26, 29–33, 39]. Eight studies reported non-significant differences in serum Pb concentrations in AD patients and controls [17, 18, 29–33, 39] and four reported higher Pb serum concentrations in AD patients [16, 23, 25, 26].

Five studies measured Pb plasma concentrationsof AD patients and controls [15, 19, 27, 37, 38]. Four reported that the Pb plasma concentrations were not significantly different between AD patients and controls [15, 19, 27, 37] and one reported higher Pb plasma concentrations [38].

In the meta-analysis, this section included 1042 AD patient samples and 1657 control samples (16 studies). The findings obtained from the random effect model revealed there was no noticeable variation in the Pb concentrations between individuals with AD and those without the disease (Hedges' g, 0.38; 95% CI, −0.09, 0.85; $p=0.110$) (Fig. 4). The pooled studies were heterogeneous ($I^2=96.78$, $Q=152.01$, $p<0.001$). There was publication bias based on Egger's regression test results ($z=3.05$, $p=0.0023$). Subgroup analysis indicated a higher concentration of Pb in the AAS method (Hedges' g, 2.03; 95% CI, 0.63, 3.42; $p=0.004$) and developing countries (Hedges' g, 1.83; 95% CI, 0.9, 2.76; $p<0.001$) in AD patients compared to healthy controls.

Furthermore, meta-regression analyses explained that age ($\beta=-0.02$, $p=0.82$) and gender (female) ($\beta=-0.004$, $p=0.98$) had no statistically significant impact on Pb concentrations.

Mercury (Hg)

Eighteen studies measured Hg concentrations in the body fluids of AD patients and healthy controls [15, 16, 21–23, 27, 29–38, 40, 41].

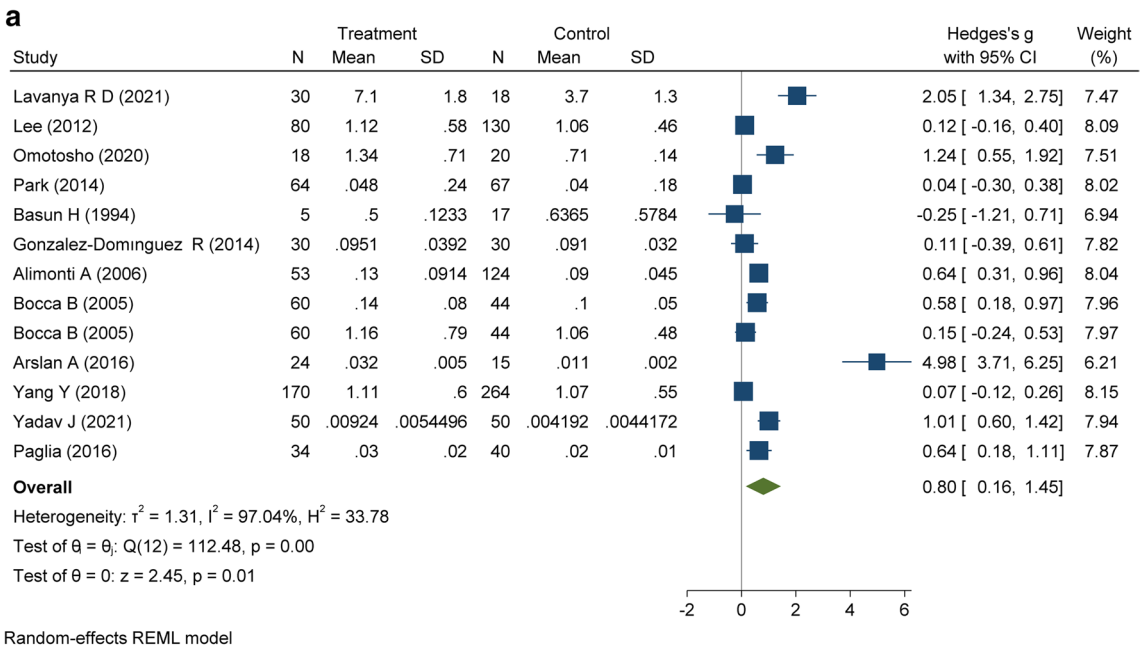


Fig. 2 **a**, **b** Point and pooled estimates of Hedge's *g* effect size, along with 95% confidence intervals for the concentration of Cd in patients with AD when compared to healthy controls in the subgroups of different body fluids (plasma, serum, whole blood) and assessment methods (AAS, ICP). Additionally, heterogeneity indices and the *p*-value for Cochran's *Q*-test of heterogeneity are provided (Cd, cadmium; AD, Alzheimer's disease; ICP, individually coupled plasma; AAS, atomic absorption spectrometry; HDI, human development index; K, number of studies)

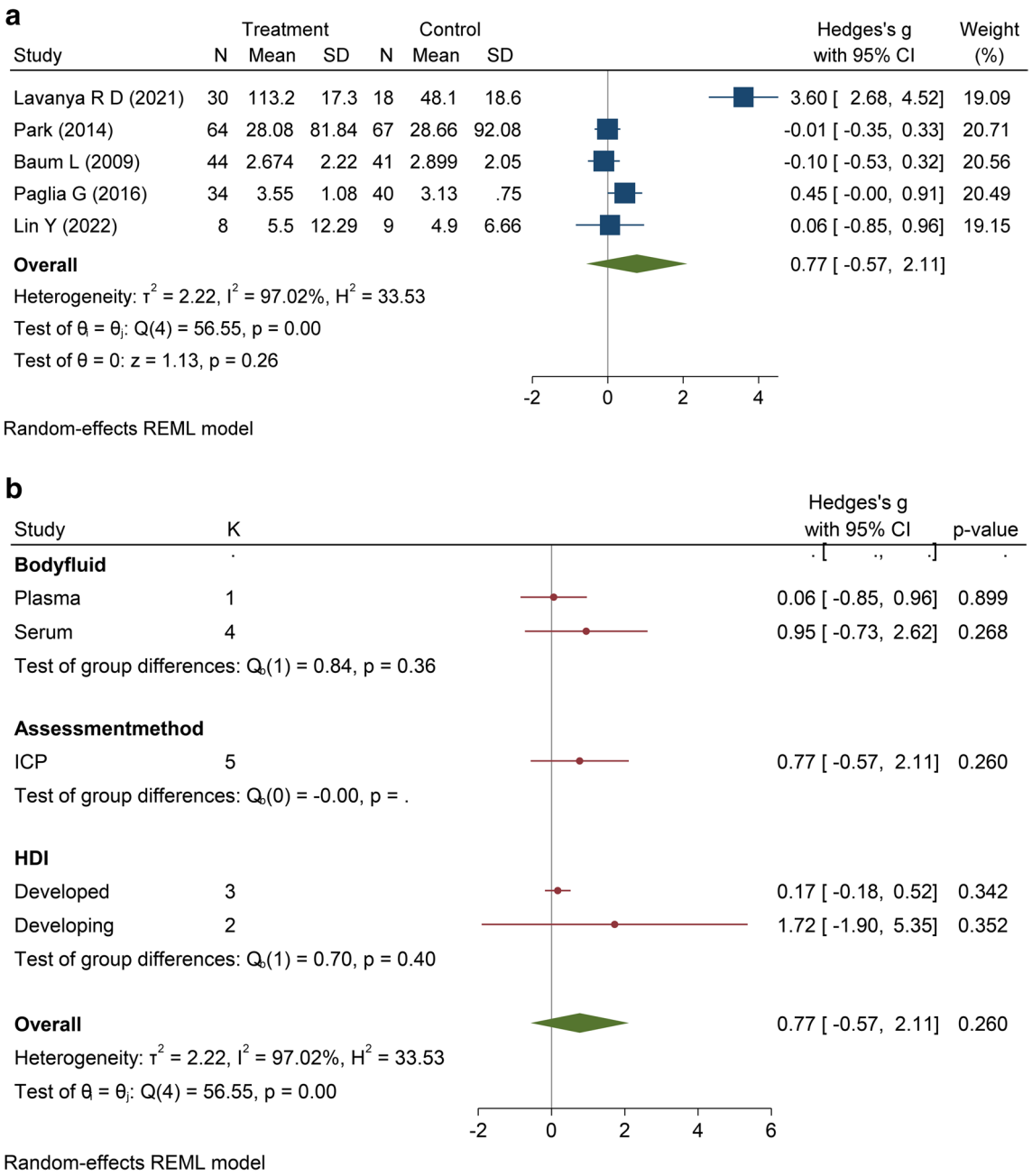


Fig. 3 **a**, **b** Point and pooled estimates of Hedge's *g* effect size, along with 95% confidence intervals for the concentration of As in patients with AD when compared to healthy controls in the subgroups of different body fluids (plasma, serum, whole blood) and assessment method (ICP). Additionally, heterogeneity indices and the *p*-value for Cochran's *Q*-test of heterogeneity are provided (As, arsenic; AD, Alzheimer's disease; ICP, individually coupled plasma; HDI, human development index; K, number of studies)

Three studies measured CSF mercury concentrations and reported non-significant results [15, 27, 34].

Among seven studies that measured Hg whole blood concentrations [21, 22, 31, 33, 35, 36, 40], one reported lower [33] and two reported higher [21, 31] Hg concentrations [22, 35] in AD patients compared to controls. Other studies reported non-significant results [21, 31, 36, 40].

Seven studies measured serum Hg concentrations [16, 23, 29–33]. One reported lower [30] and three reported higher serum Hg concentrations in AD patients [1, 32, 33]. On the other hand, three studies indicated no significant change in serum Hg concnetrations between individuals with AD and those without the disease [16, 23, 33].

Among three studies that measured plasma Hg concentrations [15, 37, 38], two reported a non-significant result [37,

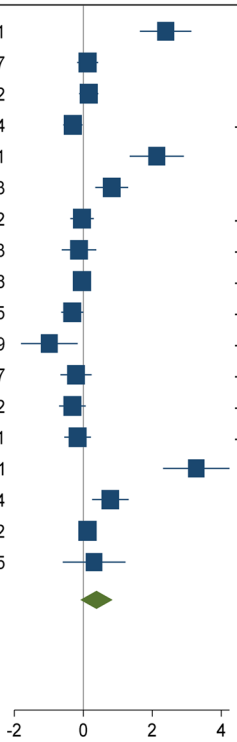
a

Study	Treatment N	Treatment Mean	Treatment SD	Control N	Control Mean	Control SD	Hedges's g with 95% CI	Weight (%)
Lavanya R D (2021)	30	312.8	74.8	18	150.2	51	2.39 [1.64, 3.13]	5.19
Gerhardsson L (2008)	173	2.6758	5.0761	54	2.074	3.8387	0.12 [-0.18, 0.43]	5.84
Lee (2012)	80	2	2.7	130	1.7	1.2	0.16 [-0.12, 0.43]	5.86
Lee (2012)	80	19	9.7	130	21.9	9.4	-0.30 [-0.58, -0.02]	5.86
Omotosho (2020)	18	138.5	29.6	20	83.2	21	2.13 [1.34, 2.92]	5.12
Fathabadi (2018)	27	222.2	285.7	54	78.8	66.3	0.82 [0.35, 1.30]	5.64
Park (2014)	64	1.52	11.28	67	1.96	10.72	-0.04 [-0.38, 0.30]	5.80
Gonzalez-Domınguez R (2014)	30	.0454	.0308	30	.0496	.0353	-0.13 [-0.63, 0.37]	5.60
Hare D J (2016)	206	.262	.604	758	.297	.938	-0.04 [-0.19, 0.11]	5.95
Alimonti A (2006)	53	.4295	.3505	124	.5265	.2775	-0.32 [-0.64, 0.00]	5.82
Giacoppo (2014)	15	14.04	11.09	10	24.6	9.109	-0.99 [-1.81, -0.17]	5.05
Paglia G (2016)	34	.13	.09	40	.16	.17	-0.21 [-0.67, 0.24]	5.66
Bocca B (2005)	60	.44	.27	44	.52	.22	-0.32 [-0.71, 0.07]	5.75
Bocca B (2005)	60	47.3	22.5	44	50.9	20.1	-0.17 [-0.55, 0.22]	5.75
Arslan A (2016)	24	.37	.12	15	.053	.011	3.27 [2.31, 4.24]	4.77
Zhang S (2010)	50	32.42	14.12	20	22.79	3.94	0.78 [0.25, 1.31]	5.56
Yang Y (2018)	170	2.5	1.35	264	2.36	1.02	0.12 [-0.07, 0.31]	5.93
Lin Y (2022)	8	.43	1.05	9	.18	.35	0.31 [-0.60, 1.22]	4.87
Overall							0.38 [-0.09, 0.85]	

Heterogeneity: $\tau^2 = 0.95$, $I^2 = 96.78\%$, $H^2 = 31.10$

Test of $\theta = \theta_j$: Q(17) = 152.01, p = 0.00

Test of $\theta = 0$: z = 1.60, p = 0.11



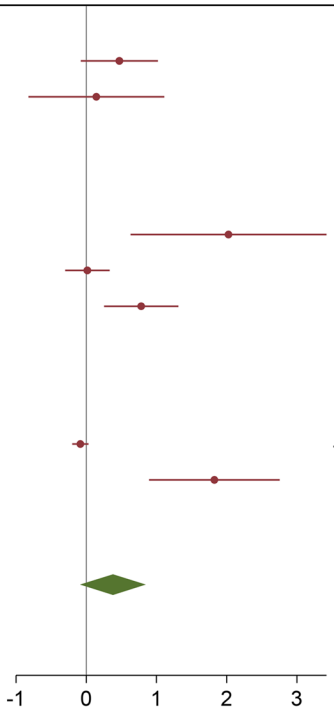
Random-effects REML model

b

Study	K	Hedges's g with 95% CI	p-value
Bodyfluid			
Serum/Plasma	13	0.47 [-0.08, 1.02]	0.092
Whole blood	5	0.14 [-0.82, 1.11]	0.771
Test of group differences: $Q_b(1) = 0.33$, p = 0.56			
Assessmentmethod			
AAS	3	2.03 [0.63, 3.42]	0.004
ICP	14	0.02 [-0.30, 0.33]	0.922
NM	1	0.78 [0.25, 1.31]	0.004
Test of group differences: $Q_b(2) = 12.17$, p = 0.00			
HDI			
Developed	13	-0.08 [-0.20, 0.03]	0.161
Developing	5	1.83 [0.90, 2.76]	0.000
Test of group differences: $Q_b(1) = 15.93$, p = 0.00			
Overall		0.38 [-0.09, 0.85]	0.110

Heterogeneity: $\tau^2 = 0.95$, $I^2 = 96.78\%$, $H^2 = 31.10$

Test of $\theta = \theta_j$: Q(17) = 152.01, p = 0.00



Random-effects REML model

◂**Fig. 4** a, b Point and pooled estimates of Hedge's *g* effect size, along with 95% confidence intervals for the concentration of Pb in patients with AD when compared to healthy controls in the subgroups of different body fluids (plasma, serum, whole blood) and assessment methods (AAS, ICP). Additionally, heterogeneity indices and the *p*-value for Cochran's *Q*-test of heterogeneity are provided (Pb, lead; AD, Alzheimer's disease; ICP, individually coupled plasma; AAS, atomic absorption spectrometry; HDI, human development index; K, number of studies; NM, not mentioned)

38], while others reported higher Hg concentrations in AD patients [15].

Regarding the meta-analysis, among 714 AD patient samples and 1046 control samples (13 studies), there was no significant difference between these two groups (Hedges' *g*, 0.35; 95% CI, − 0.65, 1.35; $p = 0.492$) (Fig. 5). The pooled studies were heterogeneous ($I^2 = 99.03$, $Q = 569.78$, $p < 0.001$).

The Egger's regression test did not reveal any evidence of publication bias ($z = 1.81$, $p = 0.0697$). Results in subgroup analysis indicated higher Hg concentrations in AD patients in developing countries compared to healthy controls (Hedges' *g*, 1.84; 95% CI, 0.78, 2.91; $p = 0.001$). Furthermore, meta-regression analyses explained that age ($\beta = 0.06$, $p = 0.17$) and gender (female) ($\beta = -0.02$, $p = 0.21$) had no statistically significant impact on Hg concentrations.

Discussion

Heavy metals have a well-documented history as risk factors for myriad diseases, including various cancers, autoimmune diseases, and neurocognitive disorders [42–45]. Data on four commonly implicated toxic heavy metals were gathered.

Our analysis indicated that there is a significant increase in Cd levels in the blood of individuals with AD compared to healthy controls. Furthermore, the subgroup analysis indicated a significant elevation in of serum Cd concentrations when employing the ICP method. However, Cd concentrations measured using the ICP method showed tighter confidence intervals than those measured using AAS. Additionally, we added a subgroup analysis based on the Human Development Index (HDI) sorted by the International Monetary Fund (IMF) and the United Nations (UN) [46]. Our HDI subgrouping indicated that developing and developed countries have statistically higher circulatory Cd concentrations in AD patients than in healthy controls. This finding requires further investigation. One hypothesis is that higher Cd concentrations might be related to poor regulation and increased exposure to industrial Cd in developing countries [47]. Cd has garnered increasing attention due to exposure through tobacco smoking and food products. Tobacco can cause the accumulation of considerable Cd in smokers, while polluted soil and water can lead to Cd accumulation in plants and crops [48]. The exact mechanism of Cd pathogenicity in inducing AD has not been clearly illustrated; however, evidence suggests Aβ formation as a primary pathological contributor to AD [49]. An increase in the level of these toxic metals is capable of leading to AD pathogenicity. The Cd excretion rate is relatively low and can increase the BBB's permeability [50]. Cd can also interfere with neurotransmitters [50], which are capable of increasing dopamine and 5-hydroxytryptamine (5-HT) in specific brain regions, as shown in animal models [51].

Arsenic is associated with carcinogenic effects [52]. Although the pathogenicity hypothesis of As in AD is not robust, with the exact mechanism unestablished, some studies propose cell proliferation and DNA-methylated oxidative stress. Altered DNA repair may be closely associated with these effects [52]. It has also been proposed that As can invoke brain inflammatory responses and cause tau and Aß formation [53]. It triggers the generation of reactive oxygen species (ROS) and impairs mitochondrial function in brain tissue. This fact leads to the activation of apoptotic pathways, causing neuronal cell death and brain tissue degeneration [54]. The outcomes of our study suggest there is no significant alteration in As concentrations among individuals with AD compared to healthy individuals, as observed in the subgroups. Due to the limited number of studies, this metal subgrouping has relatively larger confidence intervals and none of the subgrouping was significant.

Lead is a historically well-known toxic metal that can cause brain white matter damage and cell death [55]. Exposure can affect multiple organ systems, namely the cardiovascular, renal, and reproductive systems [56]. Studies showed that Pb can enter BBB by calcium channels and has an approximate half-life of two years. After entering the brain tissue, Pb can suppress neurotransmitter release and cause neural death by oxidative stress pathways [57]. Pb can substitute for calcium in various cellular processes, leading to the impairment of tight junctions and increased permeability of the BBB [58]. This phenomenon allows for the enhanced entry of Aβ peptides into the brain, which play a crucial role in AD pathogenesis [59]. In addition, some studies have suggestedt an increase in Pb concentrations can lead to DNA methylation and neurodegenerative diseases, including AD [56]. Although our overall analysis indicated that circulatory Pb concentrations are not significantly different between AD patients and controls, residents of developing countries—specifically India, Turkey, and Iran—tend to demonstrate higher Pb concentrations in their AD patients. This phenomenon has not been well studied, however, we hypothesize that this may be related to more common industrial exposures and weaker regulatory measures in said countries [7]. Further, using the AAS method, Pb concentrations were significantly higher in AD patients than in healthy individuals with a wide confidence interval.

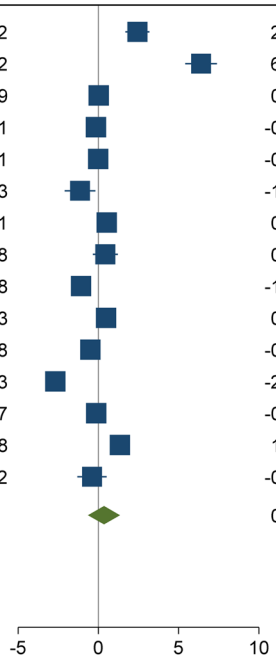
a

Study	Treatment N	Treatment Mean	Treatment SD	Control N	Control Mean	Control SD	Hedges's g with 95% CI	Weight (%)
Lavanya R D (2021)	30	223.1	33.5	18	102.5	67.2	2.43 [1.68, 3.19]	6.57
Hock C (1997)	33	2.64	.38	65	1.09	.12	6.40 [5.41, 7.39]	6.39
Lee (2012)	80	1.45	.77	130	1.43	.89	0.02 [-0.25, 0.30]	6.78
Lee (2012)	80	2.93	1.79	130	3.23	2.1	-0.15 [-0.43, 0.13]	6.78
Park (2014)	64	1.46	6.48	67	1.54	8.51	-0.01 [-0.35, 0.33]	6.77
Fung (1995)	9	.4	.3	9	.76	.3	-1.14 [-2.10, -0.19]	6.42
Alimonti A (2006)	53	1.7228	.8459	124	1.3259	.7201	0.52 [0.20, 0.85]	6.77
Giacoppo (2014)	15	5.415	5.803	10	3.326	1.698	0.43 [-0.35, 1.22]	6.55
Paglia G (2016)	34	.32	.27	40	.62	.28	-1.08 [-1.56, -0.59]	6.71
Bocca B (2005)	60	1.78	.79	44	1.41	.73	0.48 [0.09, 0.87]	6.75
Bocca B (2005)	60	4.24	3.22	44	5.85	3.18	-0.50 [-0.89, -0.11]	6.75
Cho J (2017)	108	1.914	.14	216	2.184	.073	-2.68 [-2.99, -2.37]	6.78
Yang Y (2018)	170	8.45	8.46	264	9.77	10.37	-0.14 [-0.33, 0.06]	6.80
Yadav J (2021)	50	.02332	.0073609	50	.00834	.0138168	1.34 [0.91, 1.77]	6.73
Lin Y (2022)	8	.8	5.92	9	3.2	5.62	-0.40 [-1.31, 0.52]	6.45
Overall							0.35 [-0.65, 1.35]	

Heterogeneity: $\tau^2 = 3.81$, $I^2 = 99.03\%$, $H^2 = 102.94$

Test of $\theta_i = \theta_j$: Q(14) = 569.78, p = 0.00

Test of $\theta = 0$: z = 0.69, p = 0.49



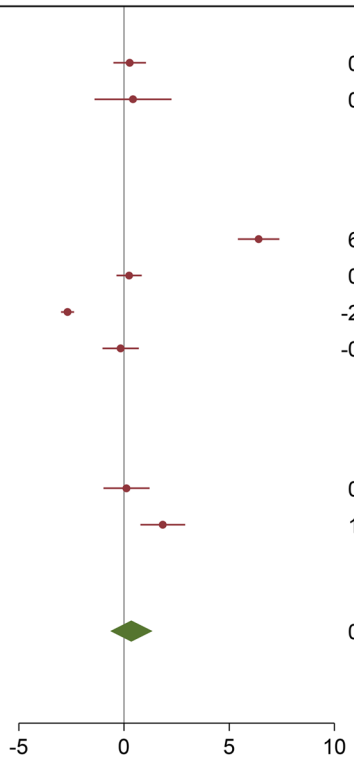
Random-effects REML model

b

Study	K	Hedges's g with 95% CI	p-value
Bodyfluid			
Serum/Plasma	7	0.27 [-0.51, 1.05]	0.495
Whole Blood	8	0.43 [-1.40, 2.26]	0.647
Test of group differences: $Q_b(1) = 0.02$, p = 0.88			
Assessmentmethod			
AAS	1	6.40 [5.41, 7.39]	0.000
ICP	10	0.24 [-0.36, 0.85]	0.428
NM	1	-2.68 [-2.99, -2.37]	0.000
others	3	-0.16 [-1.02, 0.70]	0.716
Test of group differences: $Q_b(3) = 342.15$, p = 0.00			
HDI			
Developed	13	0.12 [-0.98, 1.21]	0.835
Developing	2	1.84 [0.78, 2.91]	0.001
Test of group differences: $Q_b(1) = 4.91$, p = 0.03			
Overall		0.35 [-0.65, 1.35]	0.492

Heterogeneity: $\tau^2 = 3.81$, $I^2 = 99.03\%$, $H^2 = 102.94$

Test of $\theta_i = \theta_j$: Q(14) = 569.78, p = 0.00



Random-effects REML model

◂**Fig. 5** **a**, **b** Point and pooled estimates of Hedge's *g* effect size, along with 95% confidence intervals for the concentration of Hg in patients with AD when compared to healthy controls in the subgroups of different body fluids (plasma, serum, whole blood) and assessment methods (AAS, ICP). Additionally, heterogeneity indices and the *p*-value for Cochran's *Q*-test of heterogeneity are provided (Hg, mercury; AD, Alzheimer's disease; ICP, individually coupled plasma; AAS, atomic absorption spectrometry; NM, not mentioned; HDI, human development index; K, number of studies)

Developing countries again indicated that the Pb concentrations are higher in AD patients than in controls. Though, as previously discussed, there is limited evidence requiring further investigation regarding this association [60].

No significant change was observed in the circulating Hg concentrations among individuals with AD except in two studies performed in Iraq, the only developing country measuring Hg concentrations that showed slightly higher concentrations in AD patients compared to controls. Despite this, Hg has been proposed to influence AD pathogenesis. Major Hg sources include anthropogenic sources, fish consumption, nature exposure, and vaccines [61, 62]. In addition, experimental studies have shown that in some concentrations, Hg may be associated with increased oxidative stress pathways, the creation of neurofibrillary tangles, glutathione consumption, and Aß formation [61]. Hg, particularly in its organic form (methylmercury), can cross the BBB and accumulate in the brain. This metal impairs mitochondrial function and disrupts synaptic transmission, which can lead to neuronal dysfunction and even death [12]. Similar to the other metals, the subgroup analysis of Hg concentrations showed that the ICP method again demonstrated a smaller confidence interval and non-significant differences verus the AAS method. The developing countries demonstrated a significant increase in Hg concentrations in AD patients compared to controls. In body fluid subgrouping, there was no significant difference between AD and controls Hg concentrations in any of the measured fluids.

Another noteworthy result of this meta-analysis pertains to the HDI subgroup analysis. Our results indicated that pooled data for developing countries had wider confidence intervals with all four toxic heavy metals of interest than developed countries' relatively narrow confidence intervals. This conclusion may be influenced by stricter protocols and advanced equipment indeveloped countries in measuring blood heavy metal concentrations versus developing countries.

Previous studies on this review had limitations, and therefore, our study willfurther contextualize this subject matterr. Previous reviews included less related data, and the results, as a study published previously, included 14 studies on toxic metals while we included 27 studies. Also, a similar previous study did not include As in the toxic metals. We also used new subgrouping methods, such as HDI, which had not been discussed previously.

Limitations

There are several limitations in our systematic review and meta-analysis. The results should be interpreted cautiously, considering the variation in outcomes with different methods and high heterogeneity. Future prospective studies are warranted to evaluate circulatory toxic heavy metals concentrations (measuring intended metals with ICP and AAS methods to obtain more reliable results) and their potential pathogenic roles in AD patients. Another limitation of our study is the possible bias that the diagnosis of AD in different studies may cause. There is no other way to improve this bias; however, we recommend that AD diagnoses be predicated upon up-to-date, evidence-based clinical criteria.

Conclusion

Our findings demonstrated a potential relationship between higher overall Cd concentrations, higher Hg concentrations in developing countries, and Pb concentrations with AD pathogenicity. Conversely, the circulatory concentrations of As were similar in AD patients and healthy controls. These findings may be used for larger-scale prospective studies to assess heavy metal concentrations and their physiological roles and implications in AD patients. It is essential to establish safety thresholds and interpretations of the heavy metal concentrations in various body fluids and continuously reduce or mitigate toxic heavy metal sources as AD prevalence rises. Our results demonstrate that developing countries exhibit higher correlations between the heavy metals of interest and AD occurrence. Therefore, early comprehensive screenings may be effective interventions as secondary prevention measures that can help identify risk factors, aid in source control, and inform more timely diagnosis and management.

Author Contribution AK, SN, OM, AN, RF, and SK participated in the creation, planning, and writing of the manuscript. AK, SN, AA, RF, and SK were responsible for collecting and analyzing the data, as well as providing input for its interpretation. They played roles in gathering and examining the information, and all authors (AK, SN, OM, RF, AN, SK, VV, and AA) contributed to the drafting and critical review of the manuscript, ensuring its intellectual integrity. The final version of the manuscript was reviewed and approved by all authors.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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