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REVIEW

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Exposure to heavy metals and neurocognitive function in adults: a systematic review

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Abstract

Exposure of individuals to heavy metals (HMs) is a growing concern with far-reaching implications for human health. HMs encompass a diverse range of elements that, when present in excess or in particular chemical forms, have the potential to elicit adverse effects on the central nervous system and cognitive function. This systematic review aims to comprehensively investigate the relationship between exposure to HMs and neurocognitive function in adults. The methodological framework for this review adheres rigorously to the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines. A meticulous and extensive search strategy was executed within PubMed and Web of Science, specifically targeting articles published in the English language until the cutoff date of December 5, 2023. The evaluation of the retrieved studies was systematically conducted by employing the assessment approach outlined by (Gascon et al. in Environ Int 86 60 67, 2016). The initial search yielded a substantial pool of 1573 articles, culminating in a refined selection comprising eight pertinent studies, collectively enrolling a participant cohort totalling $n = 1,828,126$. Notably, the studies under review predominantly manifested a cross-sectional or cohort design and were geographically situated within the continents of North America and Asia. Furthermore, it is imperative to underscore that a predominant and recurring observation emanating from the majority of the scrutinized investigations underscores a significant correlation between exposure to cadmium (Cd) and mercury (Hg) and deleterious neurocognitive outcomes in the adult population. In summary, our systematic review postulates that exposure to HMs through various routes of exposure harbors the potential for adverse effects on adult neurocognitive function; however, it is incumbent upon future research endeavors to validate and corroborate these findings through further empirical exploration.

Keywords Heavy metals, Neurocognitive function, Metal exposure, Cadmium, Mercury

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Introduction

In recent decades, scientific research has made remarkable strides in understanding the intricate associates between environmental factors and human health [18, 22, 23, 39, 42, 43]. Among the various agents that exert a profound influence on health outcomes, potentially toxic elements (PTEs) including heavy metals (HMs) have emerged as a significant concern, particularly due to their ubiquitous presence in the environment and their potential to impact human health [23, 36]. Toxic elements (e.g., HMs) encompass a group of elements, such as lead (Pb), mercury (Hg), cadmium (Cd), arsenic (As), and chromium (Cr), which can exert toxic effects on living organisms at relatively low exposure levels [11, 38, 51, 52]. These elements have been widely studied in the context of environmental pollution and their adverse health effects, including cardiovascular diseases, cancer, and developmental abnormalities [54, 61, 67]. Moreover, emerging evidence suggests that HMs may also have a profound impact on neurocognitive function, particularly in adults [68].

Neurocognitive function refers to a set of interconnected cognitive processes, including memory, attention, executive function, language, and visuospatial abilities, that collectively enable individuals to perceive, process, and respond to information from their environment [24]. Disruptions in these cognitive functions can have significant implications for an individual's quality of life, productivity, and overall well-being [71, 72]. While the neurotoxic effects of certain HMs, such as Pb and Hg, have been extensively studied in the context of pediatric populations, there is a growing body of evidence suggesting that HMs exposure may also impact neurocognitive function in adults [21, 30, 34, 48, 55, 57, 58, 66]. This emerging area of research raises critical questions about the potential long-term consequences of chronic HMs exposure on cognitive ageing, dementia risk, and overall cognitive health in adulthood [66]. Mechanistically, HMs can exert their neurotoxic effects through a variety of pathways. One prominent mechanism involves oxidative stress and the generation of reactive oxygen species, which can lead to damage to cellular components, disruption of signaling pathways, and impaired neuronal function. HMs can also interfere with neurotransmitter systems, disrupt calcium homeostasis, and alter gene expression patterns, further contributing to their neurotoxic potential. Additionally, HMs can cross the blood–brain barrier and accumulate in brain tissues, potentially affecting various regions critical for neurodevelopment, such as the hippocampus, prefrontal cortex, and cerebellum [7, 32].

We are not aware of any review study on the association between exposure to HMs and neurocognitive function in adults. Therefore, this paper aims to provide a comprehensive overview of the current state of knowledge regarding the intricate relationship between exposure to HMs and neurodevelopment. By examining the existing literature, elucidating mechanistic insights, and highlighting gaps in our understanding, this review aims to contribute to the ongoing discourse surrounding the impact of HMs on neurocognitive outcomes.

Search methodology and selection procedures

In adherence to the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines as outlined by Stroup et al. (2000), this review was conducted [10]. A systematic inquiry of relevant literature was carried out across PubMed, and Web of Science databases to identify all pertinent articles investigating the correlation between HMs with neurocognitive function in adults, encompassing publications up to December 5, 2023. The search strategy incorporated specific keywords associated with HMs and neurocognitive function, irrespective of the publication date, as detailed in Additional file 1: Table S1 within the Additional file Materials. Furthermore, a comprehensive analysis of reference lists from identified papers was undertaken to identify any additional relevant articles. The search employed the use of "OR" operators between HMs keywords as well as neurocognitive function keywords, with the results of exposure and outcome being connected using the "AND" operator. The entire search process was independently conducted by two authors, and any uncertainties were resolved through collaborative discussions between the authors.

Inclusion and exclusion parameters

This systematic review primarily centered on observational research designs, specifically including cohort, cross-sectional, and case–control studies, that were published in the English language. The review encompassed various types of heavy metals (HMs) exposure, which encompassed occupational, dietary, and exposure to ambient HMs. Diverse methods for assessing HMs exposure were considered. The primary focus of the study was on evaluating neurocognitive function in adults. To maintain the focus within these inclusive criteria, animal studies, reviews, clinical trials, and studies related to neurodevelopment in children were excluded from the analysis. The review provides comprehensive information, both in terms of general study characteristics and methodological details, along with the presentation of association metrics, such as beta-coefficient (β), correlation coefficient (r), odds ratio (OR), relative risk (RR), and others, for each study, as detailed in Table 1.

Table 1 Main characteristics of studies included in the systematic review

	Authors (date)	Location	Study population	Sample size	Age	Definition of exposure	Exposure, concentration	Study design	Cognitive function indices	Measure of association type	Measure of association (95% CI)
1	Smith, et al. [58]	USA Columbus, Ohio	Volunteers employed in two mercury cell chlor-alkali plants	A total of 98 workers	Mean (standard deviation) of subjects age 42.1 ± 13.4 years	Exposure to elemental mercury and urinary mercury concentration	Among the cohort of 98 elementary concentration workers, the average urinary mercury concentration stood at 0.14 ± 0.14 mg/l, while in the current group of 28 individuals, it registered slightly elevated at 0.18 mg/l ± 0.17 mg/l	Cohort	Short-term memory capacity (1: Wechsler digit span forward, 2: precise measurement of the STM Span—the 50% threshold)	Correlation	The second measure assessed a worker's 50% threshold for correct serial recall and revealed a significant decrease in short-term memory capacity with higher elemental mercury exposure. This was observed in a study involving 26 workers with urinary mercury levels ranging from 0–20 to 0–51 mg/1. A follow-up study with 60 different workers, despite lower urinary mercury levels (0–11 mg/1 on average), confirmed the link between urine mercury levels and reduced short-term memory capacity

Table 1 (continued)

	Authors (date)	Location	Study population	Sample size	Age	Definition of exposure	Exposure, concentration	Study design	Cognitive function indices	Measure of association type	Measure of association (95% CI)
2	van Wijngaarden, et al. [66]	Seychelles	Participants of the Seychelles Child Development Study (SCDS)	533	19 years old	Prenatal methyl mercury exposure	The mean prenatal methylmercury (MeHg) exposure, quantified through maternal hair analysis, amounted to 6.89 (4.52) parts per million (ppm). Conversely, the recent postnatal MeHg exposure, evaluated through children's hair samples, exhibited a higher average of 10.29 (6.06) ppm	Cohort	The research conducted an evaluation of neurodevelopment and behavior through a variety of assessments. These included mood assessment using the Profile of Mood States—Bipolar (POMS-Bi), fine motor control examination with Finger Tapping, cognitive ability assessment using the Kaufman Brief Intelligence Test (K-BIT), evaluation of motor skills through measures of fine motor control and complex perceptual motor control, and the assessment of visual perception and sensitivity using Visual Spatial Contrast Sensitivity	Linear regression	Prenatal exposure to methylmercury (MeHg) did not exhibit any negative correlations with the evaluated endpoints. In contrast, recent postnatal MeHg exposure was linked to adverse outcomes. These included diminished Finger Tapping performance in women and lower scores on the K-BIT Matrices test for both genders, irrespective of adjustments made for polyunsaturated fatty acids (PUFA)
3	Sallon, et al. [55]	India and China	The study comprised volunteers who were fluent Tibetan speakers, spanning an age range from 18 to 65 years. The assessment of mercury (Hg) exposure drew from a prior pilot investigation (Group 1) that involved a comparison of urinary Hg levels between individuals using Hg in the form of Tsothel in Precious Pills and those utilizing other variants of traditional medicine (Group 2). Moreover, data on population-based background Hg exposure (Group 3) served as a reference point for the analysis	120	18 and 65 years	Urinary Hg levels, Blood Hg level	Urinary Hg (μg/L): Group 1; mean (SD): 1.5 ± 1.24 Group 2; mean (SD): 1.57 ± 0.55 Group 3; mean (SD): NA Blood Hg (μg/L): Group 1; mean (SD): 0.22 ± 0.19 Group 2; mean (SD): 0.18 (± 0.11) Group 3; mean (SD): 0.35(± 0.35)	Cross-sectional	Neurocognitive testing (Standardized Mini-Mental State Examination (MMSE))	Mean difference	Regarding neurocognitive testing, no statistically significant distinctions were discerned among the groups concerning the Wechsler Memory Scale, Grooved Pegboard, and Visual Retention. Nevertheless, in the case of Mini-Mental, Brief Word Learning, and Verbal Fluency assessments, participants in Group 1 demonstrated superior scores, even after adjusting for potential confounding variables

Table 1 (continued)

	Authors (date)	Location	Study population	Sample size	Age	Definition of exposure	Exposure, concentration	Study design	Cognitive function indices	Measure of association type	Measure of association (95% CI)
4	Li, et al. [30]	USA	US adults aged 60 years or older	2068	Adults aged 60 years or older	Blood cadmium levels	The study participants exhibited a median blood cadmium concentration of 0.35 µg/L, with an interquartile range (IQR) spanning from 0.24 to 0.56 µg/L	Cross-sectional,	Cognitive function was evaluated through various assessments, encompassing the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Learning Test, the CERAD Word List Recall Test, the Animal Fluency Test, and the Digit Symbol Substitution Test (DSST). These assessments were likely selected to appraise diverse facets of cognitive performance, including memory, verbal fluency, and processing speed	Multiple linear regression models	Blood cadmium levels, when considered as a continuous variable, displayed an inverse association with the composite z-score (µg/L, β = −0.11, 95% CI −0.20 to −0.03). Similarly, when blood cadmium levels were categorized into quartiles, a significant association was evident. Participants in the upper quartile of exposure (blood cadmium ≥ 0.63 µg/L) exhibited somewhat lower composite z-scores compared to those in the lower quartile of exposure (blood cadmium < 0.25 µg/L) (µg/L, β = −0.14, 95% CI −0.25 to −0.03), and this pattern demonstrated a statistically significant trend across the quartiles of blood cadmium levels (P < 0.0001)
5	Geier, et al. [21]	USA	The study examined a total of 1,821,663 individuals aged between 60 and 80 years old, whose blood samples from the 2011–2012 National Health and Nutrition Examination Survey revealed detectable levels of blood ethylmercury (ethyl-Hg)	1,821,663	Ages of 60 and 80 years	Blood ethyl-Hg levels	Blood mercury levels (µg/L) Mean Ethylmercury ± std (range) = 0.3 ± 0.2 (0.16–1.0) Mean Methylmercury ± std (range) = 4.0 ± 5.3 (0.08–23.2) Mean Inorganic mercury ± std (range) = 0.4 ± 0.3 (0.2–2.8)	Cross-sectional,	Cognitive function scores were determined using the following assessments: Consortium to Establish a Registry for Alzheimer's Disease–Word List Learning (CERADW-L) delayed recall test Animal Fluency Test Digit Symbol Substitution Test	Logistic regression modeling/ odds ratios	A notably higher risk for reduced scores on the Animal Fluency Test (odds ratio (OR) = 13.652, p = 0.0029) and the CERAD W-L delayed recall test (OR = 6.401, p = 0.0433) was observed among individuals in the higher ethylmercury (ethyl-Hg) exposure group when compared to those in the lower ethyl-Hg exposure group

Table 1 (continued)

	Authors (date)	Location	Study population	Sample size	Age	Definition of exposure	Exposure, concentration	Study design	Cognitive function indices	Measure of association type	Measure of association (95% CI)
6	Mao, et al. [34]	USA	The study involved a total of 3,231 participants from the CARDIA (Coronary Artery Risk Development in Young Adults) study	3231	18–30 years of age	Toenail mercury and selenium levels	Toenail selenium at exam Y2 (ppm): 0.86 ± 0.15 Toenail mercury at exam Y2 (ppm): 0.32 ± 0.37	Cohort	Cognitive function was assessed using the Rey Auditory Verbal Learning Test (RAVLT), the Digit Symbol Substitution Test (DSST), and the Stroop test	The general linear regression model	The research aimed to explore the isolated impacts of toenail selenium (Se) and mercury (Hg) levels on cognitive function tests; however, no significant associations were detected after accounting for potential confounding factors. Furthermore, the study investigated whether the interaction between toenail Se and Hg levels affected cognitive function, especially concerning LCv-3 PUFA (long-chain omega-3 polyunsaturated fatty acids) intake. It is worth noting that this interaction did not attain statistical significance
7	Peng, et al. [48]	China	375 older men aged 60–74 years in Guangxi, China	375	Aged 60–74 years (mean age: 66.0 years)	Urinary Cd concentrations	The median urinary Cd concentration of all participants was 1.58 mg/g creatinine	Cross-sectional	Cognitive function was evaluated through the utilization of the Chinese version of the Mini-Mental State Examination (MMSE). Cognitive impairment was identified based on education-specific cutoff points established for MMSE scores	General linear regression and logistic regression models	Urinary cadmium (Cd) levels exhibited an inverse association with MMSE scores, with a beta-coefficient of − 0.76 and a 95% confidence interval (CI) ranging from − 1.28 to − 0.23 for a twofold increase in urinary Cd. Moreover, a twofold rise in urinary Cd was linked to an elevated risk of cognitive impairment, as indicated by an adjusted odds ratio (OR) of 1.46 and a 95% CI ranging from 1.14 to 1.86

Table 1 (continued)

	Authors (date)	Location	Study population	Sample size	Age	Definition of exposure	Exposure, concentration	Study design	Cognitive function indices	Measure of association type	Measure of association (95% CI)
8	Silman, et al. [57]	Upper Amazonian, Peru	Matsigenka communities residing within the Manu National Park (MNP) along the Manu River include Maizal, Cacaotal, and Yomibato	38	Average years (SD) 29 (13.8)	Samples of blood and hair. Mercury Exposure/Word Span	Hg (ppm): mean (SD) = 7.05 (2.40)	Cross-sectional	The study encompassed the customization of working memory tasks to align with the Matsigenka culture and language. This adaptation included evaluations for verbal storage (Word Span), visuospatial storage (Corsi Block Task), and the assessment of executive functions through the Self-Ordered Pointing Task (SOPT). Furthermore, a modified iteration of the Trail Making Tests A & B (TMT A & B) was subjected to a pilot test to explore its potential as a measure of executive function	Ordinary least squares multiple linear regression	Word Span Accuracy: − 0.01 (− 0.03, 0.01) Corsi Block Accuracy: − 0.04 (− 0.06, − 0.01) SOPT Errors: 0.23 (0.05, 0.42)

Evaluation of the quality of articles

To gauge the caliber of each encompassed article, we employed an 8-point assessment checklist (see Additional file 1: Tables S2, S3), a framework that has been previously employed in systematic reviews concerning the human health repercussions of environmental exposures [20, 37]. Each criterion was subject to a potential score ranging from 0 to 1 or 0 to 2, culminating in a maximum cumulative score of 11. The entirety of scores garnered by a particular study was translated into a percentage, representing the proportion of the possible highest score achievable by that study. The subsequent categorization of study quality was predicated on the derived percentage. As such, percentages exceeding 81% were classified as excellent quality, those spanning 61–80% were deemed of good quality, the range of 41–60% indicated fair quality, while scores within 21–40% denoted poor quality; finally, those achieving less than 20% were categorized as very poor quality. The appraisal of quality was independently executed by the authors, with conclusive consensus reached through mutual agreement.

Results

Retrieved articles and their attributes

A total of 1573 articles were initially obtained through our primary search, encompassing 3 instances of duplication. Following the screening of article titles, 126 articles were selected for abstract assessment (Fig. 1). After reviewing abstracts, 99 articles were excluded, and subsequently, 19 articles were eliminated during the full-text review, culminating in a final inclusion of eight articles ($n=1,828,126$ participants) for comprehensive evaluation in our review.

Detailed characteristics of the studies featured in our review are delineated in Table 1. Within the eight selected studies, three (37.5%) adopted a cohort design [34, 58, 66] and five (62.5%) employed a cross-sectional approach [21, 30, 48, 55, 57]. Predominantly, the studies ($n=2$) were executed in Asia [48, 55], with four studies conducted in the USA [21, 30, 34, 58], one study in Africa [66] and one study taking place in Latin America [57] (Fig. 2).

The evaluation of exposure was based on various parameters across the studies. Most of studies analyzed HMs in body fluids, including urine and blood [21, 30, 48, 55, 58]; one study measured HMs in toenail [34], one study based on hair samples [66] and one study used blood sample along with hair samples [57] to assess exposure to HMs.

In the analyzed studies, the primary focus of neurocognitive function assessment centered on short-term memory capacity, specifically utilizing the Wechsler digit span forward test and a precise measurement known as the STM Span, employing a 50% threshold. Furthermore, the study integrated adaptations of working memory tasks tailored to the cultural and linguistic context of the Matsigenka population. These customizations included evaluations for verbal storage (Word Span), visuospatial storage (Corsi Block Task), and assessments of executive functions through the Self-Ordered Pointing Task (SOPT). Additionally, an adapted version of the Trail Making Tests A & B (TMT A & B) was explored as a potential measure of executive function. The comprehensive assessment of cognitive function in these investigations included a diverse array of cognitive tests. Notably, the Profile of Mood States—Bipolar (POMS-Bi) was employed to gauge mood, and fine motor control was assessed using the Finger Tapping test. Cognitive abilities were appraised through the application of the Kaufman Brief Intelligence Test (K-BIT). The evaluation of motor skills encompassed measures of fine motor control and complex perceptual motor control. Visual perception and sensitivity were scrutinized using the Visual Spatial Contrast Sensitivity test. Furthermore, in select reviewed studies, the Standardized Mini-Mental State Examination (MMSE) was utilized as a neurocognitive assessment tool. In addition to the aforementioned assessments, the battery of cognitive function tests encompassed the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Learning Test, the CERAD Word List Recall Test, the Animal Fluency Test, and the Digit Symbol Substitution Test (DSST). These diverse tests were thoughtfully selected to investigate distinct facets of cognitive performance, spanning memory, verbal fluency, and processing speed. Moreover, cognitive function scores were derived from various sources, including the Consortium to Establish a Registry for Alzheimer's Disease–Word List Learning (CERADW-L) delayed recall test, the animal fluency test, and the Digit Symbol Substitution Test. Furthermore, the neurocognitive function was evaluated through the Rey Auditory Verbal Learning Test (RAVLT), the Digit Symbol Substitution Test (DSST), and the Stroop test in the scrutinized studies.

Assessment of study quality

Across the individual studies, the comprehensive quality scores exhibited a range from five (45.5%) to eight (72.2%) (see Additional file 1: Table S4). Within this spectrum, three studies achieved a "good" rating, and five studies were deemed of "fair" quality. Notably, the criteria that yielded the highest scores included "Confounding factors", "Statistics", "Potential bias" and "effect size" (all studies achieving a score of 1), "Exposure assessment"

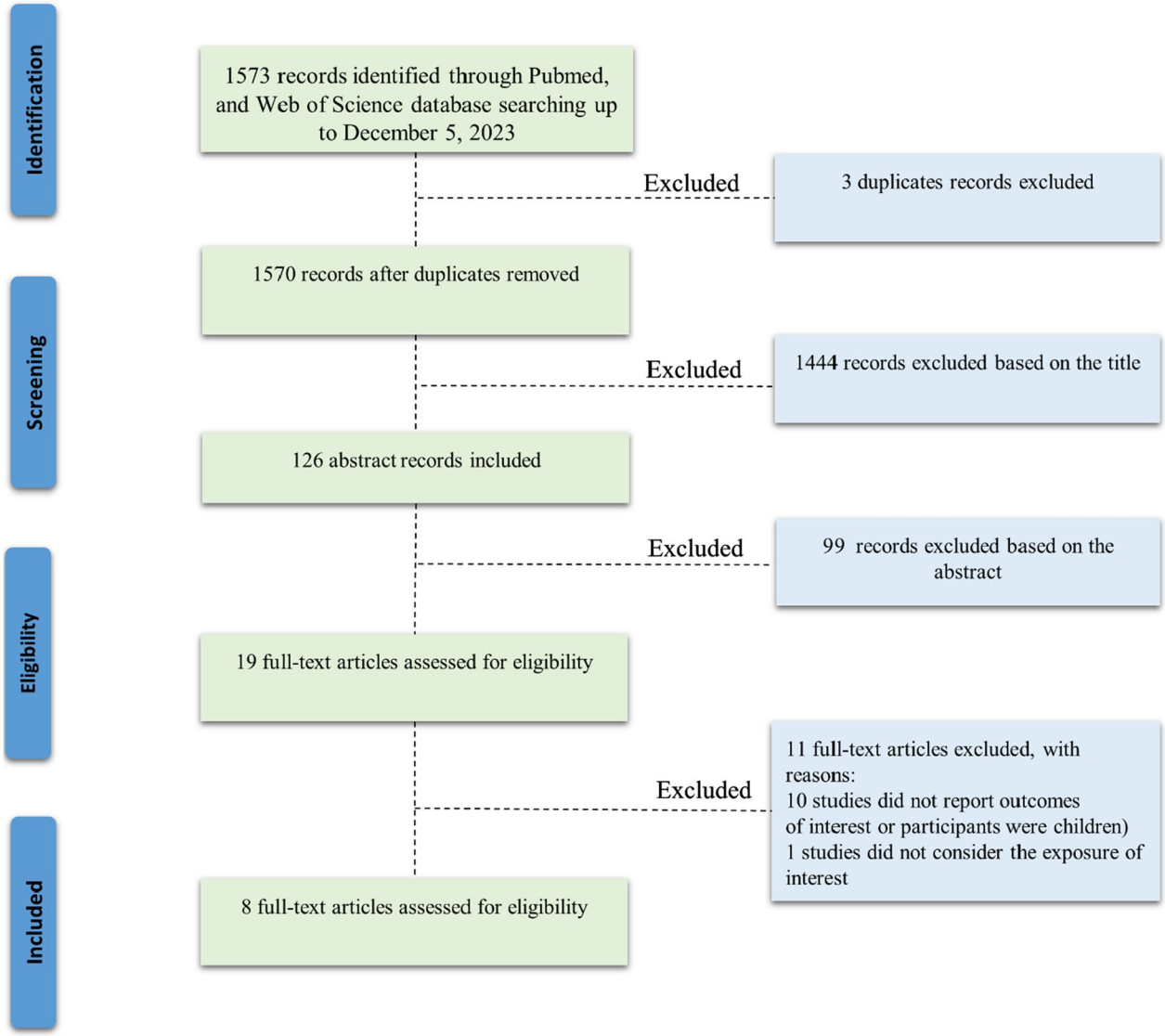

Fig. 1 Flow diagram of systematic review

(with three studies receiving a score of 2), and "Study design" (with three studies receiving a score of 2).

Reported results by reviewed studies

In the reviewed studies, a consistent theme emerged, indicating an association between heavy metal (HM) exposure and diminished neurocognitive function in adults. Specifically, Smith et al. [58] revealed a significant reduction in short-term memory capacity linked to increasing elemental mercury exposure. This finding was corroborated by a replication study involving another group of 60 workers, where despite lower urinary mercury concentrations, a statistical association persisted, connecting urine mercury levels to decreased short-term memory capacity [58]. In contrast, van Wijngaarden et al. [66] did not identify adverse associations between prenatal methylmercury (MeHg) exposure and the measured endpoints. However, for recent postnatal MeHg exposure, adverse associations emerged, notably affecting Finger Tapping (non-dominant hand) among women and the Kaufman Brief Intelligence Test (K-BIT) Matrices for both sexes [66]. Sallon et al. [55] presented an intriguing perspective, suggesting that mercury-containing Tibetan Medicine may not entail appreciable adverse effects and could potentially have beneficial impacts on neurocognitive function [55]. Likewise, Li et al. [30] reported an inverse relationship between blood cadmium levels and

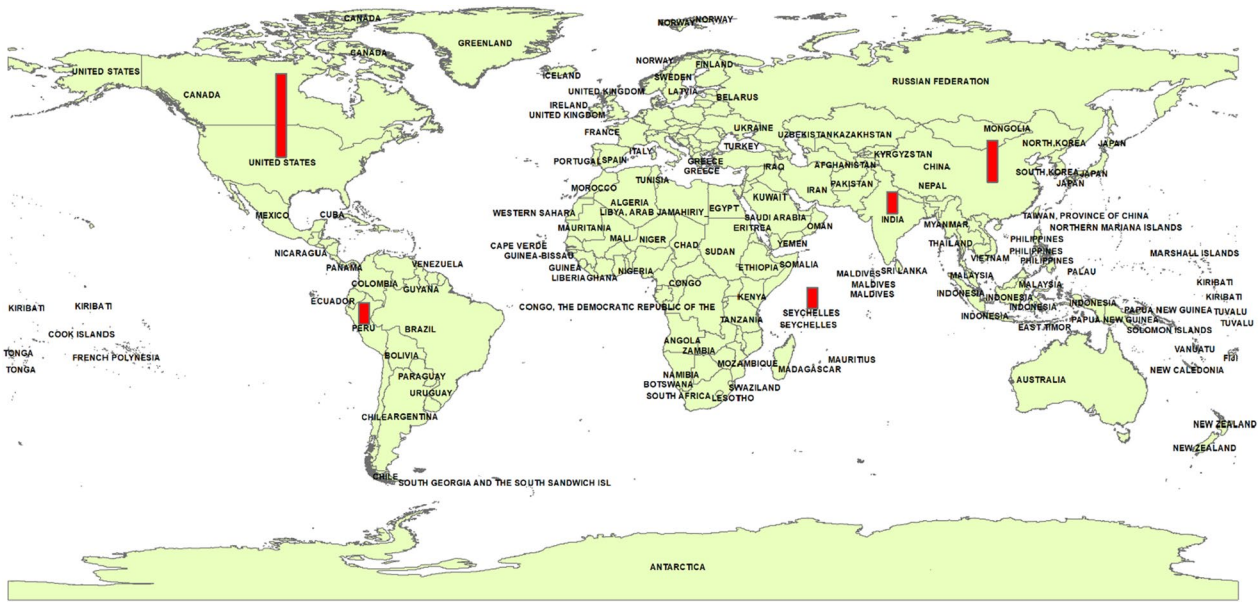

Fig. 2 Distribution of reviewed studies in the world map and number of studies in each country

composite cognitive z-scores, with higher blood cadmium levels associated with lower composite cognitive scores [30]. Geier et al. [21] observed significantly increased risks for lower scores in animal fluency tests and CERAD W-L delayed recall tests among individuals with higher ethylmercury exposure [21]. However, Mao et al. [34] did not find significant associations between toenail selenium (Se) and Hg levels and cognitive function. They did, however, note a notable association between long-chain omega-3 polyunsaturated fatty acids (LCv-3 PUFA) intake and Digit Symbol Substitution Test (DSST) scores, particularly among individuals with higher toenail Se levels [34]. Peng et al. [48] unveiled an inverse association between urinary Cd levels and MMSE scores, with a twofold increase in urinary Cd linked to a heightened risk of cognitive impairment [48]. Finally, Silman et al. [57] reported significant associations between hair Hg levels and cognitive performance, albeit with varying degrees of magnitude depending on the type of cognitive task. Specifically, Hg exposure was negatively associated with executive functioning and visuospatial performance, while education emerged as the sole predictor of Word Span accuracy [57]. In conclusion, these collective findings underscore the intricate interplay between HM exposure and adult neurocognitive function, revealing both adverse associations and intriguing nuances.

Discussion

To our awareness, this represents the inaugural investigation that systematically reviewed the association between HMs exposure and adults' neurocognitive function. Our comprehensive review encompassed 1573 titles published in the English language until December 5, 2023. The evaluation of quality indicated that three studies achieved a "good" rating, while five studies were classified as "fair" quality. Most of the reviewed studies reported an adverse effect on neurocognitive function in adults due to exposure to Hg and Cd. However, prenatal exposure to Hg was not associated with lower cognitive scores in adulthood. Moreover, one study reported no significant association between Se and Hg with neurocognitive function. Moreover, they reported that these elements did not have any interaction role in the association of LCv-3 PUFA with cognitive function.

Exposure evaluations

Within our analysis, three studies explored HMs utilizing urine samples [48, 55, 58], and three studies relied on blood HM concentration measurements [21, 30, 57]. An additional study opted for hair samples [66] and toenail samples [34] to examine the relationship between exposure to HMs and neurocognitive function. Comparatively, urine-based exposure assessment offers certain merits over blood samples. Urine collection is a noninvasive method, making it generally preferable to participants over the invasive nature of blood collection. Furthermore, the extraction and analysis of HMs in urine samples are relatively less complex than those in blood samples. Nonetheless, it is important to recognize that urine HM levels signify exposure within the past 24 h, contrasting with blood samples that reflect prolonged exposure to HMs [33, 35]. Exposure evaluation through

hair and nail samples presents advantages, including the simplicity of sampling, even surpassing urine samples, along with its noninvasive nature and ability to indicate long-term exposure. However, the detection of HMs demands larger amounts of samples, and existing evidence indicates a weaker correlation between external HMs exposure and hair and nail HMs levels when compared to levels in urine and blood [16, 41].

The evaluation of metal exposure through biological samples is a complex process with ongoing discussions and evolving methodologies. For instance, in the assessment of mercury exposure, urine analysis is often deemed suitable for inorganic forms, while blood and hair samples are preferred for organic forms [1, 73]. The selection of the most appropriate biological sample depends on the chemical form of the metal in question. In the case of arsenic, measuring total arsenic in any biological sample may not provide a comprehensive evaluation of exposure; instead, it is recommended to assess specific chemical forms containing the element [65, 74]. However, it is crucial to acknowledge the dynamic nature of exposure assessment, particularly for metals like manganese and zinc [15, 64]. There is an ongoing discourse within the scientific community regarding the optimal biological sample for assessing exposure to these metals. The choice between urine, blood, hair, and nail samples may vary based on the specific metal and its chemical forms. External contamination remains a challenge, particularly with hair and nail samples, emphasizing the need for meticulous sample collection and analysis protocols [25, 45].

In our comprehensive review, we recognize the nuances and debates surrounding exposure assessment methodologies. While our review encompassed studies utilizing diverse biological samples, including urine, blood, and hair, we acknowledge that the choice of sample type may influence the observed associations. Further research is warranted to refine exposure assessment techniques and address potential limitations associated with each biological sample, ensuring a more nuanced understanding of the intricate relationship between metal exposure and health outcomes.

Evaluation of study outcomes

In the reviewed studies, a diverse array of cognitive function tests was employed to comprehensively assess neurocognitive function in adults. These tests presented a spectrum of advantages and limitations, each tailored to probe specific cognitive domains. The Wechsler Digit Span Forward Test [69], characterized by its quick administration, offered a convenient means of gauging short-term memory capacity. However, its scope was relatively narrow, primarily focusing on memory without delving into broader cognitive processes. Conversely, the STM Span [13] with a 50% Threshold exhibited precision in measuring short-term memory span, capable of detecting subtle differences. Nevertheless, its specificity to short-term memory limited its ability to assess other cognitive functions comprehensively. The Word Span test contributed valuable insights into verbal memory and storage capacity, offering a lens into language-related cognitive abilities. Still, its confined focus on verbal aspects left other cognitive domains unexplored. Similarly, the Corsi Block Task [9], concentrating on visuospatial memory and storage, served as a valuable tool for understanding spatial cognition. Nonetheless, its emphasis on visuospatial aspects restricted its examination of broader cognitive functions. The Self-Ordered Pointing Task (SOPT) [53] ventured into executive functions, encompassing working memory and cognitive flexibility. This allowed for the exploration of higher-order cognitive processes. However, its complexity and potential interpretational challenges warranted careful consideration. The Trail Making Tests A & B (TMT A & B) [63] emerged as robust measures of executive functions, including cognitive flexibility and attention. These tests proved effective in identifying deficits associated with various neurological conditions. Nevertheless, their relatively intricate nature and susceptibility to motor skill influence called for comprehensive evaluation. The inclusion of the Profile of Mood States—Bipolar (POMS-Bi) [59] provided valuable insights into mood assessment, a vital facet of cognitive health and emotional well-being. However, the test's primary focus on mood limited its direct assessment of cognitive functions, which can be influenced by diverse factors. The Kaufman Brief Intelligence Test (K-BIT) [28] assessed cognitive abilities encompassing verbal and non-verbal skills, offering a glimpse into overall intellectual functioning. Despite its comprehensiveness, the K-BIT may not capture specific cognitive domains in depth, and its administration could be time-consuming. Fine motor control and complex perceptual-motor control measures were essential for evaluating motor skills and coordination, which play a pivotal role in daily functioning. However, these tests were inherently less focused on assessing cognitive functions and may not fully encapsulate the cognitive aspects of motor control. The Visual Spatial Contrast Sensitivity test [44] scrutinized visual perception and sensitivity, a critical element for spatial awareness and overall cognition. It also had the potential to uncover visual impairments affecting cognitive performance. Nevertheless, its primary focus on visual perception made it less suitable for assessing broader cognitive domains. The MMSE [14], a widely used tool, rapidly detected global cognitive

function and cognitive impairment. However, its limited capacity to delve into specific cognitive domains made it less suitable for tracking subtle cognitive changes over time. Lastly, the CERAD tests [27], including the Word List Learning and Word List Recall tests, were tailored for assessing memory and language-related cognitive functions. These tests proved valuable for tracking cognitive decline in Alzheimer's disease. Nevertheless, their focus on specific cognitive domains necessitated the inclusion of other tests to provide a comprehensive understanding of neurocognitive function. The diverse array of cognitive function tests employed across the reviewed studies underscores the complexity of assessing neurocognitive function. In navigating this complexity, we carefully considered the advantages and limitations inherent in each chosen tool. For instance, the Wechsler Digit Span Forward Test offered a quick assessment of specific cognitive aspects, albeit with a focused scope primarily on memory [17, 60]. This specificity, observed in several tests such as the Self-Ordered Pointing Task (SOPT) and Visual Spatial Contrast Sensitivity test, allowed for in-depth exploration of executive functions and visual perception, respectively. However, these benefits came with the recognition of potential interpretational challenges and the need for careful consideration [3]. Tests like the Trail Making Tests A & B emerged as robust measures of executive functions. Nevertheless, their relatively intricate nature and susceptibility to motor skill influence highlighted the importance of a comprehensive evaluation strategy. Combining tests tailored to memory, language-related functions, executive functions, and mood assessment, could provide a holistic understanding of neurocognitive function [4]. While this approach allowed for a multifaceted examination, the observed variability in test selection prompts reflection on the implications for future neurocognitive research. Consideration of standardized batteries or harmonization efforts may enhance the comparability of findings across studies, contributing to the robustness of the field [70]. In summary, the selection of cognitive function tests should be aimed to strike a delicate balance between their advantages and limitations, contributing to a nuanced understanding of neurocognitive function in adults. This comprehensive approach acknowledges the multifaceted nature of cognitive health and provides insights for future research endeavors in the field.

Potential mechanisms

Exposure to heavy metals can have a range of potential mechanisms that affect neurocognitive function in adults [2, 6, 29, 31, 49, 56]. While the exact mechanisms can vary depending on the specific HMs involved, some common pathways and mechanisms include: (i) Oxidative stress: many heavy metals, including lead, mercury, and cadmium, can induce oxidative stress in the brain. They generate reactive oxygen species (ROS) that overwhelm the body's antioxidant defences, leading to oxidative damage to neurons and other brain cells. This oxidative stress can disrupt normal cellular function and contribute to cognitive impairments [47]. (ii) Inflammation: heavy metal exposure can trigger an inflammatory response in the brain. The activation of microglia, the immune cells of the central nervous system, can lead to the release of pro-inflammatory cytokines and chemokines. Chronic inflammation in the brain is associated with cognitive decline and neurodegenerative diseases [62]. (iii) Neurotransmitter disruption: some heavy metals can interfere with neurotransmitter systems. For example, mercury can bind to and inhibit the function of neurotransmitter receptors, disrupting synaptic transmission and impairing cognitive processes like learning and memory (Carmona, Roudeau, & Ortega, [12]). (iv) Disruption of blood–brain barrier (BBB): heavy metals can compromise the integrity of the blood–brain barrier, a protective barrier that regulates the passage of substances between the bloodstream and the brain. A compromised BBB can allow heavy metals to enter the brain more easily, increasing their neurotoxicity (Archie, Al Shoyaib, & Cucullo, [5]). (v) Neuroinflammation: chronic exposure to heavy metals can lead to persistent neuroinflammation, characterized by increased activation of immune cells and the release of inflammatory mediators within the brain. This sustained neuroinflammation can contribute to neuronal damage and cognitive dysfunction [46]. (vi) Alteration of neurotrophic factors: heavy metals can disrupt the balance of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), which play a crucial role in promoting neuronal growth, survival, and plasticity. Dysregulation of these factors can impair cognitive function [8]. (vii) Impaired synaptic plasticity: heavy metals may interfere with synaptic plasticity, the ability of synapses to strengthen or weaken over time in response to learning and experience. Disrupted synaptic plasticity can lead to cognitive deficits [19]. (viii) Accumulation in specific brain regions: some heavy metals tend to accumulate in specific brain regions, such as the hippocampus and frontal cortex, which are critical for learning, memory, and executive functions. Accumulation of heavy metals in these regions can directly impair cognitive processes [40]. (ix) Epigenetic modifications: heavy metals can induce epigenetic changes in the brain, altering the expression of genes involved in neuronal function and plasticity. These epigenetic modifications can have long-lasting effects on

cognitive function [26]. (x) Neurodegenerative pathways: chronic heavy metal exposure has been associated with the activation of neurodegenerative pathways, such as those involved in Alzheimer's and Parkinson's diseases [50]. This suggests that heavy metals may contribute to the development of neurodegenerative conditions with cognitive impairment. It is important to note that HMs can have both acute and chronic effects on neurocognitive function, and the mechanisms can be complex and multifaceted. The specific mechanisms may vary depending on factors such as the type of HM, the duration and level of exposure, individual susceptibility, and other environmental and genetic factors. Further research is needed to fully elucidate the precise mechanisms by which different HMs impact neurocognitive function in adults.

Limitations

Although our evaluation of quality revealed three studies with good scores, it is essential to recognize certain limitations within these investigations, which warrant consideration in future research endeavors. Primarily, the observational nature of the reviewed studies hinders the establishment of a definitive causal link between HMs exposure and neurocognitive function. Additionally, the utilization of urine samples in some studies to gauge HMs exposure raises concerns about its adequacy as a gauge for long-term exposure to these pollutants. Furthermore, the majority of prior studies omitted assessments of exposure pathways and sources of HMs, a critical aspect for comprehending the toxicity of diverse metals. Furthermore, the scope of HMs evaluation in most of the reviewed studies was restricted, and the collective impact of exposure to a mixture of HMs on neurocognitive function has yet to be explored. Turning to limitations within our review, it is imperative to acknowledge the geographical distribution of studies primarily focused on Asia, and the USA, with only a study conducted in Latin America as well as one study in Africa, conspicuously omitting representation from Europe, and Australia.

Conclusion and recommendations for future research

In this systematic review, we meticulously screened 1573 articles, ultimately including eight studies with 1,828,126 participants. The studies, varying in design and geographic focus, utilized diverse exposure assessments, including body fluids and samples like toenails and hair. Most of the reviewed studies were classified as "fair" quality. Consistent findings across the studies indicated an association between HMs exposure and diminished neurocognitive function in adults. Specific observations included reduced short-term memory capacity with increasing elemental Hg exposure, an inverse relationship between blood Cd levels and composite cognitive z-scores, and an association between urinary Cd levels and MMSE scores. However, nuanced perspectives, such as Tibetan Medicine potentially having beneficial impacts, added complexity to the overall narrative. While acknowledging the limitations inherent in our study, its findings cast a valuable light on the association between HMs exposure and decreased neurocognitive function, thereby offering insights for policymakers and decision-makers striving to mitigate these unfavorable health impacts.

Our recommendations for future research involve comprehensive evaluations of HMs exposure, encompassing both internal and external measurements from diverse sources (e.g., water, food, air, and soil samples). This should include an assessment of all potential exposure pathways, encompassing ingestion, dermal contact, and inhalation routes. Additionally, the application of advanced analytical techniques with enhanced sensitivity, such as inductively coupled plasma mass spectrometry (ICP-MS), can significantly expand the scope of HMs evaluation in forthcoming studies. To enhance the precision and accuracy of internal exposure assessment, we suggest concurrent evaluation across distinct biological samples (such as blood, urine, nails, and hair) in future investigations. Furthermore, the utilization of advanced statistical methodologies to examine the synergistic effects of HMs mixture exposure on health outcomes can augment the reliability of findings. Additionally, future research endeavors should take into consideration potential heterogeneity in population age. The existing literature primarily focuses on adults, and exploring the impact of heavy metal exposure on neurocognitive function across different age groups, including adolescents and the elderly, could provide a more nuanced understanding of these associations. Age-related variations in susceptibility and response to heavy metal exposure may exist, and considering these factors can contribute to a more comprehensive assessment of the diverse population dynamics. This approach will not only enhance the generalizability of findings, but also guide targeted interventions for specific age groups vulnerable to the neurocognitive effects of heavy metal exposure.

Supplementary Information

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Additional file 1: Table S1. Search keywords and protocols in different databases. **Table S2.** Criteria for quality assessment of the studies*. **Table S3.** Characteristics of the studies on exposure to HMs and neurocognitive function. **Table S4.** Quality Assessment Results.

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Availability of data and materials
This is a review and all data are publicly available.

Declarations

Ethics approval and consent to participate
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Competing interests
None.

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