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Exposure to heavy metals and neuropsychological performance in children with and without attention deficit hyperactivity disorder (ADHD)

Sharanpreet Kaur[1,2], Josefa Canals-Sans[1,2,3,7]✉, Paula Morales-Hidalgo[1,2], José A. Alda[4,5] & Victoria Arija[1,3,6,7]

Heavy metal exposure can negatively impact the neuropsychological development of children and has been linked to ADHD. We investigated the association between heavy metal exposure and neuropsychological functions in children with and without ADHD. Urine samples were collected from 205 children aged 6–16 years (66 without ADHD, 139 with ADHD). Neuropsychological assessments were conducted using WISC-IV/V and CPT-2/3. Associations between Pb, Cd, Cu, As, Hg and neuropsychological outcomes were analysed using multiple linear regressions. In the overall sample, Cu was negatively associated with processing speed (β=-6.75, 95% CI:-13.42–(-0.08)), with this effect being more pronounced in ADHD children (β=-11.54 and −12.52, 95% CI:-21.53–(-3.51)). In ADHD children, Pb (β=-11.23, 95% CI:-21.24–(-1.23)) was negatively associated with processing speed. Hg exposure was linked to CPT indicators of inattentiveness, both in overall and ADHD samples (higher detectability, commission error, omission error and slower reaction times scores). In ADHD children, Pb exposure was associated with increased commission errors (β = 5.41, 95% CI:0.89–9.39) and Cu with omission errors (β = 8.44, 95% CI:-0.02–16.89) and faster reaction time (β = 7.43, 95% CI:1.21–13.65). Our findings highlight the potentially harmful effects of Cu, Pb, and Hg on neuropsychological performance in children, with these associations being particularly pronounced among ADHD children. The findings call for public health strategies aimed at reducing environmental exposure to heavy metals in children to promote optimal neuropsychological development.

Keywords Heavy metals, ADHD, Neuropsychological performance, Children

Exposure to toxic heavy metals is becoming an increasing concern due to their detrimental effects on physical and mental health. This is especially true forchildren, as their developing neurons are highly sensitive to such toxins, which can cause potential impairment in their neuropsychological development[1–3]. The exposure to heavy metals such as lead (Pb), arsenic (As), cadmium (Cd), mercury (Hg), excessive copper (Cu), and their negative effects are well known[4]. These heavy metals, by accumulating in specific areas of the brain, such as the frontal cortex and hippocampus, impact children's executive functioning, memory, and learning. They also interfere with epigenetics by modifying gene expression responsible for neural plasticity and functionality, which can increase cognitive impairment, potentially contributing to attention deficit hyperactivity disorder

[1]Nutrition and Mental Health Research Group (NUTRISAM), Universitat Rovira i Virgili (URV), Tarragona, Spain. [2]Research Center for Behavior Assessment (CRAMC), Department of Psychology, Faculty of Educational Sciences and Psychology, Universitat Rovira i Virgili (URV), Tarragona, Spain. [3]Institut d'Investigació Sanitària Pere Virgili (IISPV), Reus, Spain. [4]Child and Adolescent Psychiatry and Psychology, Department of Hospital Sant Joan de Déu of Barcelona, Barcelona, Spain. [5]Children and Adolescent Mental Health Research Group, Institut de Recerca Sant Joan de Déu, Barcelona, Spain. [6]Department of Basic Medical Sciences, Universitat Rovira i Virgili, Reus, Spain. [7]IU-RESCAT: University Research Institute on Sustainable, Climate Change and Energy Transition, Universitat Rovira i Virgili, Tarragona, Spain. ✉email: josefa.canals@urv.cat

(ADHD) in children[5–8]. Therefore, ADHD children may be more affected by toxic substances than those without the condition.

ADHD is a chronic neurodevelopmental disorder (NDD) with an average prevalence of 8% globally in children and adolescents[9]. The American Psychological Association defines ADHD as an early-onset neurodevelopmental disorder characterised by persistent patterns of impulsivity, inattention and hyperactivity[10]. Although genetics is the most common risk factor for its aetiology but other factors such as exposure to toxic metals are equally responsible for ADHD in children[11,12]. This has been supported by the studies that observed Pb, Cu, iAs (inorganic form of arsenic), and Cd were associated with symptoms of ADHD in children[6,13–16].

The World Health Organisation (WHO) has classified Pb, Hg, Cd and As among the top 10 non-essential elements[17]. Exposure to heavy metals can happen through contaminated food, water, surroundings and environment[18]. Studies have highlighted that Pb and Hg are highly neurotoxic metals, i.e., even in small amounts, can be detrimental for the neurodevelopment of children[19,20]. A systematic review highlights the negative effects of even a low level of Pb in ADHD children[21]. The impact of iAs and Cd on children's cognitive functioning has been studied, showing effects such as impaired attention and learning disabilities[22,23]. Whereas Cu is considered an essential element for growth, however, excessive consumption can have an adverse effect on cognition and ADHD[4,24,25]. This has been supported by a study conducted using the saliva of adolescents, where they found levels of Cu associated with an ADHD diagnosis[26]. In addition, prenatal and postnatal studies on As, Pb, Mn and Cd suggest impairment of memory and verbal learning in children and a reduction in IQ[27–29]. Furthermore, from the WISC-IV scale in ADHD children, it was observed that Cd correlated negatively with full IQ and Pb associated with working memory, speed processing, verbal comprehension and full IQ[6].

Although most existing studies have examined the effect of exposure to either a single heavy metal or combinations of metals on neuropsychological functioning or ADHD-related symptoms[2,28], they have not specifically assessed the impact of each metal separately on neuropsychological performance in ADHD children compared to those without any diagnosis. Moreover, to our knowledge, no such studies have been conducted in the province of Tarragona, which hosts one of the largest petrochemical complexes of Southern Europe[30]. Therefore, the present study aims to explore the potential associations between postnatal exposure to specific heavy metals (Pb, Cd, As, Hg and Cu) and neuropsychological performance in children with and without ADHD in this region.

Methods

Participants

In the current study, we analysed urine samples of 205 children: 139 ADHD children and 66 non-ADHD (no diagnosis of ADHD or autism). The age range of the children was between 6 and 16 years old, residents of the Tarragona and Barcelona provinces in Spain. Children with a diagnosis of ADHD were assessed by psychiatrists and psychologists following the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). To collect information on DSM-5 criteria for ADHD, the interview Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version was administered to the parents (K-SADS-PL)[31]. The process of the study was thoroughly explained to the parents, and their consent to participate was obtained.

Participants were part of the MetigenADHD and EPINED projects. First, MetigenADHD (Metagenomic and metabolomic profiles in ADHD children and adolescents) was an observational study conducted between 2017 and 2019 at the Hospital Sant Joan de Déu (HSJD) child psychiatry services in Barcelona, involving ADHD children. Its protocol was approved by the Ethics Committee of this Hospital (PIC-50-17). Second, EPINED (Epidemiological Research Project on Neurodevelopmental Disorders), conducted between 2014 and 2021 in schools across all the provinces of Tarragona, was a double-phase cross-sectional study. The study was ethically approved by the Reus Sant Joan University Hospital's Ethics Committee (13-10-31/10proj5). Children who were enrolled in the second phase of the study, corresponding to the individual evaluation of the child and family, had urine specimens examined. The urine sample collection and neuropsychological testing were performed concurrently. The protocol followed for ADHD assessment and diagnosis was described by Canals-Sans et al. (2021)[32].

Urine specimen collection and metal detection

A 12-ml clear polystyrene was provided to the parents of children for urine sample collection, fasting early in the morning. The sample was stored in a refrigerator until collected by the research group members. In the research laboratory, samples were centrifuged at 600 g for 10 min at 4 °C. The supernatant was stored at -80 °C in 1 ml sterile screw-cap cryotubes until transported to a specialised lab for metal concentration analysis and urine creatinine levels.

The detection of metals (Cd, Pb, As, Hg and Cu) in urine involved multiple steps. First, urine samples were diluted at a 1:10 ratio using metal standard solutions from Agilent Technologies (Santa Clara, CA, USA) in ultrapure water containing 2% nitric acid (HNO3; Merck, Darmstadt, Germany) and 1% hydrochloric acid (HCl; Merck). The diluted samples were then analysed using an Agilent 8900 triple quadrupole ICP mass spectrometer (ICP-MS; Agilent Technologies), with its performance carefully calibrated and verified. To enhance accuracy, a 400 µg/L multielement internal standard solution containing Sc (scandium), Ge (germanium), Ir (iridium), and Rh (rhodium) (ISC Science, Oviedo, Spain) was added online to the samples. Quality control procedures included reanalysing a certified reference material, Seronorm Trace Elements Urine L-1 (reference 210605; Sero, Billingstad, Norway), every 12 samples, along with a blank and an intermediate calibration standard. Additionally, the National Institute of Standards and Technology (NIST, Gaithersburg, MD, USA) Trace Elements in Natural Water Standard Reference Material SRM 1640a was used as another certified reference material and was analysed at the start and end of each sequence. To ensure consistency, one out of every twelve samples was reanalysed at the end of each session. The limits of detection (LOD) for each metal, expressed in µg/L, were as follows: Cd

= 0.03, Pb = 0.08, As = 0.5, Hg = 0.05, and Cu = 0.9. Urine creatinine levels were measured using the Sistema ADVIA 1800 and ADVIA 2400 Chemistry systems[33]. Heavy metal concentrations were adjusted according to creatinine levels (mg/dL) to minimise variation due to urine dilution. This systematic approach was designed to ensure the accuracy and reliability of the heavy metal analysis[33].

Neuropsychological tests

Wechsler Intelligence Scale for Children – Fourth and fifth edition (WISC-IV, WISC-V)[34,35]were used to measure cognitive abilities as well as the full intellectual functioning of children aged between 6 and 16 years. WISC-IV/V test is composed of several scales called main indices, such as verbal comprehension index (VCI), perceptual/fluid reasoning index (PRI/FRI), working memory index (WMI) and processing speed index (PSI). However, although WISC-IV and WISC-V have the same indices, there are some differences in the tests. PRI of the WISC-IV includes picture concepts, block design and matrix reasoning tests, and FRI of the WISC-V does not include the block design test. WISC-V has a visual spatial main index (VSI), which includes tests of visual puzzles and block design. The full intellectual quotient (FIQ) of children was obtained from WISC-IV/V. The mean score for both indexes and FIQ is 100 with a standard deviation (SD) of 15.

The Conners Continuous Performance Test – Third edition (CPT-3)[36] and the Conners' Kiddie Continuous Performance Test - second edition (K-CPT-2)[37] were used to assess neuropsychological issues related to ADHD. Both are computerised tests: the CPT-3 was administered to children aged 8 years and older, and the K-CPT-2 to those under 8. These tests measured detectability (DET; ability to detect targets from non-targets), omission (OMI; rate of missed targets), commission (COMI; incorrect responses to non-targets), hit reaction time (HRT; mean response time) and hit reaction time standard deviation (HRT-SD; consistency in reaction time). A higher score on detectability indicates poor performance, i.e., poorer discrimination. High errors on omission indicate difficulty focusing, inattentiveness. High commission errors coupled with slow reaction time indicate inattentiveness; however, when coupled with faster reaction time can indicate impulsivity. HRT is measured in milliseconds, but an uncommonly slow speed may indicate inattentiveness, and a rapid reaction can indicate impulsivity. High HRT-SD scores show higher inconsistency, suggesting the child was less engaged and inattentive. The Conners CPT-2/3 test raw scores are reverse-scored, i.e., higher scores indicate poor performance.

Covariables

In the regression analysis, we included body mass index (BMI), diet quality, age, sex and socio-economic status (SES) as potential cofounding factors. Since these factors, directly or indirectly, can play a crucial role in influencing the neuropsychological development of children, they were identified following a directed acyclic graph (DAG; Supplementary Fig. 1)[38]. The BMI of the children was calculated from the weight and height collected by a nurse or nutritionist. Additionally, the Food Consumption Frequency Questionnaire (FCFQ)[39] was completed by parents to measure their children's Spanish Diet Quality Index (SDQI)[40]. Parents also completed the sociodemographic questionnaire.

Statistical analysis

Software IBM SPSS (version 29) was used to conduct the analysis. Saphiro-Wilk test suggested data were non-parametric; therefore, urinary metal concentrations of Cd, Pb, Hg, As and Cu were log10 transformed to obtain normally distributed data. Furthermore, multiple linear regression (MLR) was performed to obtain β, 95% confidence interval (95% CI) and at a $p < 0.05$ significant level. The models were adjusted by potential covariates such as age, sex, body mass index (BMI), Spanish Diet Quality Index (SDQI), socio-economic status of the family (SES) and ADHD diagnosis. Multicollinearity among the covariates was tested with the variance inflation factor (VIF), which showed no significant multicollinearity among the covariates (sex – 1.03, age – 1.11, BMI – 1.14, SDQI – 1.02, SES – 1.09). All metals are analysed in quartiles (25, 50 and 75 percentiles) where the first quartile is used as a reference. This approach was adapted to facilitate a comparison across different exposure levels rather than treating the metal concentrations as a continuous variable. Further, in model 2, an interaction (metal × ADHD diagnosis) term was introduced. Spearman's correlation was conducted to test the correlation between urinary metals in the total sample.

Results

Table 1 lists sociodemographic characteristics and neuropsychological test data of the total sample based on the diagnosis. A 67.80% of the sample represents ADHD children. The sample was male-dominated, with a percentage of 70.24%. The mean age of the same was 10 years with a SD of 1.94 and a mean body mass index of 19.26 (SD 3.77). Most of the children were from medium (66.34%) socioeconomic status families. Furthermore, non-ADHD children performed better on both the neuropsychological tests, with a higher score observed for WISC IV/V and a lower score for CPT-2/3, as compared to ADHD children.

Furthermore, a complete descriptive statistic of urinary heavy metals for both groups can be found in Table 2. Figure 1 demonstrates the correlation between the metals for the total sample. Most of the metals have very weak correlations between them; however, a moderate correlation is observed between Cd-Cu (0.56), Pb-Cu (0.39), and Pb-Cd (0.36).

The association between urinary heavy metals and WISC-IV/V scores is detailed in Table 3. In the overall sample, the adjusted MLR model showed a negative association between PSI and Cu in the 3rd quartile (β = -6.75, 95% CI: -13.42 -0.08). On the other hand, a positive association was found for VCI and PRI/FRI with As in the 4th quartile (β = 8.19, 95% CI: 0.34–16.05 and β = 7.98, 95% CI: 1.22–14.74, respectively). No associations were found between any metals and WMI and VSI. Moreover, we did not observe any significant results between metals and FQI. Given that the diagnosis variable was significant in model 1, we introduced the interaction covariate

Variables	N	Non-ADHD – 66	ADHD – 139	p
		n (%)	n (%)	
Sociodemographic				
Sex				< 0.001
Male	144	35 (53.0)	109 (78.42)	
Female	61	31 (47.0)	30 (21.58)	
SES				0.14
Low	11	2 (3.2)	9 (7.09)	
Medium	136	43 (69.4)	93 (73.23)	
High	42	17 (27.4)	25 (19.69)	
Pharmacological treatment (ADHD)	205	-	21 (15.11%)	< 0.001
		M ± SD	M ± SD	
Age (years)	205	10.48 ± 1.07	10.24 ± 2.24	0.39
Nutritional data				
BMI (kg/cm)	205	19.05 ± 3.70	19.36 ± 3.81	0.57
SDQI score		62.92 ± 7.01	61.52 ± 6.08	0.14
Neuropsychological test				
WISC IV/V				
VCI	171	107.38 ± 11.57	97.55 ± 17.75	< 0.001
VSI	70	107.37 ± 12.92	98.66 ± 13.08	0.08
PRI/FRI	166	109.90 ± 13.60	97.59 ± 14.43	< 0.001
WMI	165	100.27 ± 13.95	89.89 ± 13.36	< 0.001
PSI	162	104.62 ± 13.28	93.73 ± 14.48	< 0.001
FIQ	180	110.77 ± 14.36	103.76 ± 18.16	0.01
Conners CPT-2/3				
DET	186	53.73 ± 8.26	56.60 ± 8.41	0.03
OMI	186	50.84 ± 10.34	58.80 ± 14.47	< 0.001
COMI	186	53.38 ± 8.28	53.43 ± 8.11	0.97
HRT	186	49.11 ± 9.56	55.72 ± 10.71	< 0.001
HRT-SD	186	51.95 ± 9.21	60.02 ± 13.02	< 0.001

Table 1. Socio-demographics and neuropsychological data by diagnosis groups. SES - socio-economic status; BMI - body mass index; SDQI - Spanish diet quality index; VCI – verbal comprehension index; VSI – visual spatial index; PRI/FRI – perceptual/fluid reasoning index; WMI – working memory index; PSI – speed processing index; FQI - full intellectual quotient; DET – detectability; OMI – omission; COMI – commission; HRT – reaction time; HRT-SD - reaction time standard deviation.

Metals (/L)	Non-ADHD		ADHD		Total	
	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)
Cd	0.04	0.05 (0.05)	0.06	0.07 (0.05)	0.05	0.06 (0.05)
Pb	0.18	0.25 (0.30)	0.31	0.34 (0.27)	0.28	0.32 (0.28)
As	20.40	46.17 (56.12)	13.04	38.91 (87.69)	16.67	41.24 (78.85)
Hg	0.35	0.47 (0.41)	0.31	0.47 (0.51)	0.32	0.46 (0.48)
Cu	3.92	4.17 (3.99)	6.52	6.80 (3.81)	5.23	5.96 (4.05)

Table 2. Distribution of urinary metals exposure. Median represents 50% percentile. Cd - cadmium; Pb - lead; As - arsenic; Hg - mercury; Cu -copper.

(ADHD × metal) in model 2. The interaction between Hg and diagnosis, and Cu and diagnoses was significant (β = -45.79, 95% CI: -87.55 – -4.04 and β = -45.86, 95% CI: -88.27 – (-3.45), respectively), indicating that the effect of Hg on VCI and Cu on the VSI is associated with the presence of ADHD. Furthermore, the adjusted MLR analyses were conducted specifically for the sample of ADHD children (See Table S1, supplementary material). Significant associations were found between PSI and Pb in the 2nd quartile (β = -11.23, 95% CI: -21.24 – (-1.23)), and Cu across all quartiles, (β between – 11.54 and – 12.52, 95% CI: -21.53 – (-3.51)). Positive associations were found for As in VCI (β = 10.76, 95% CI: 0.63–20.89) and FRI (β = 9.44, 95% CI: 0.67–18.21).

Table 4 presents the association between urinary heavy metals and CPT-2/3 scores. For the whole sample, MLR models showed a positive association between Hg and DET in the 4th quartile (β = 4.77, 95% CI: 1.07–8.48), COMI in the second quartile (β = 5.08, 95% CI: 1.43–8.73, 2nd quartile), HRT in the second quartile (β

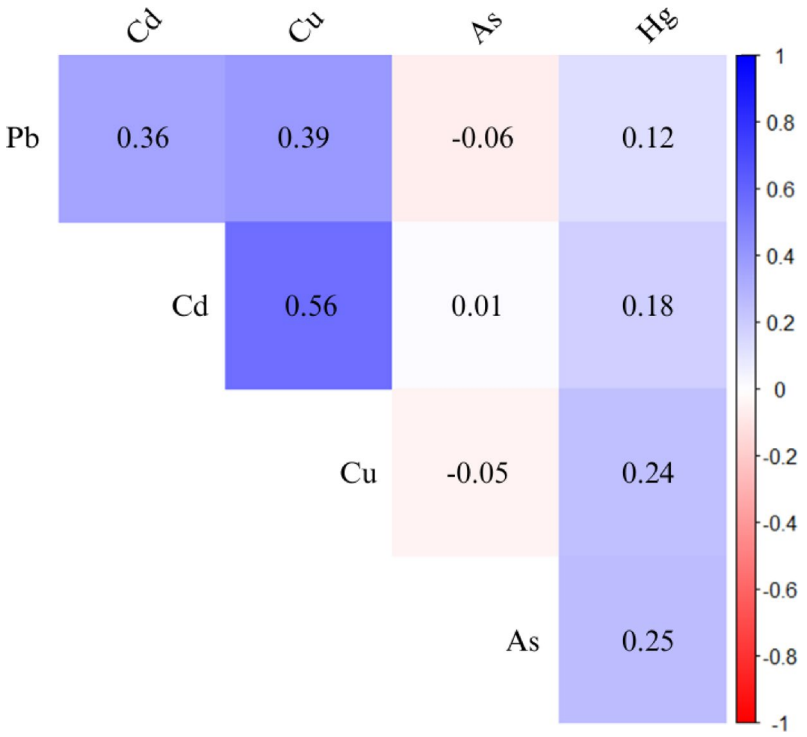

Fig. 1. Spearman correlation between the level of urinary metals in the total sample. Cd - cadmium; Pb - lead; As - arsenic; Hg - mercury; Cu - copper.

= -5.55, 95% CI: -10.13 – (-0.99)). Although the diagnosis variable was significant in model 1, the ADHD × metal covariate introduced in model 2 did not yield any significant results, indicating an independent effect of these variables on these neuropsychological variables. Only for Pb and DET (β = 36.60, 95% CI: 9.92–63.29) and COMI (β = 40.91, 95% CI: 14.93–66.88), the interaction covariate was significant, indicating an association between the two independent variables. Furthermore, adjusted MLR analyses for the sample of ADHD children (See Table S2 supplementary) showed a significant association between Hg and DET in the third quartile (β = 4.97, 95% CI: 0.87–9.07) and OMI in the 4th quartile (β = 7.62, 95% CI: 0.47–14.76). Cu in the third quartile was associated with more problems in OMI (β = 8.44, 95% CI: 0.02–16.89) and slower HRT (β = 7.43, 95% CI: 1.21–13.65). Whereas Pb is associated with higher COMI errors in the 2nd and 4th quartiles (β between 4.72 and 5.41, 95% CI: 0.41–9.93).

Discussion

In this study, we examined the potential association between postnatal exposure to urinary heavy metals (Pb, Cd, As, Hg, and Cu) and neuropsychological performance in children with and without ADHD. Our analysis of the WISC-IV/V subscales indicated that heavy metals have a more pronounced effect on the neuropsychological performance of ADHD children. Specifically, in ADHD children, processing speed was negatively impacted by Pb and Cu, with performance ratings decreasing by 11.23 units for Pb and 12.52 units for Cu. Conversely, a positive association was observed between As exposure and verbal comprehension and fluid reasoning, indicating that higher As levels were associated with better CVI and FRI. Further analysis using the CPT2/3 test subscales revealed that higher levels of Hg and Cu were associated with an increase in omission errors by 7.62 and 8.44 points, respectively, in ADHD children, indicating an association of these metals with inattentiveness. Additionally, Cu exposure was linked to a 7.43-point increase in reaction time, suggesting problems with impulsivity. Commission errors increased by 4.72 with the presence of Pb. Detectability score was affected by Hg, with an increased score of 4.97 times. Moreover, correlation across the total sample revealed moderate associations between Cd, Cu and Pb, suggesting possible shared environmental exposure sources. These findings suggest that exposure to certain heavy metals may exacerbate specific neuropsychological deficits in ADHD children.

In ADHD children, Pb is associated with decreased speed of processing performance and a higher number of commission errors. Lower processing speed scores, as observed on the WISC-V, are linked to deficits in sustained attention, high distractibility, and difficulties with organisation and planning, all common challenges for ADHD children[35]. These factors hinder their ability to process information quickly and efficiently. Additionally, the higher incidence of commission errors on the CPT3 is associated with impulsivity, poor response inhibition, and a lack of self-control, which are also hallmark neuropsychological characteristics of ADHD[41]. These findings align with previous research suggesting that Pb neurotoxicity adversely affects the central nervous system (CNS), suppresses neuroplasticity, critical for neurodevelopment, and leads to irreversible effects on

Metals	VCI		VSI		PRI/FRI		WMI		PSI	
	β	*95% CI*	*β*	*95% CI*	*β*	*95% CI*	*β*	*95% CI*	*β*	*95% CI*
Cd – Ref.	-	-	-	-	-	-	-	-	-	-
Q2 (0.04 – 0.05)	2.64	(– 4.70–10.06)	– 0.56	(– 10.96–9.83)	– 1.60	(– 8.18–4.97)	– 4.29	(– 10.36–1.78)	– 3.52	(– 10.17–3.09)
Q3 (0.05 – 0.07)	– 0.41	(– 8.07–7.24)	5.65	(– 4.95–16.25)	– 2.92	(– 9.79–3.95)	– 4.37	(– 10.72–1.97)	– 4.64	(– 11.59–2.30)
Q4 (> 0.08)	5.64	(– 2.10–13.39)	4.37	(– 7.09–15.94)	– 1.73	(– 8.59–5.14)	– 5.53	(– 11.87–0.81)	– 5.47	(– 12.39–1.45)
Model 2	-	-	-	-	-	-	-	-	-	-
Cd × Diag.	– 5.14	(– 280.15–269.87)	128.91	(– 486.71–228.89)	38.54	(– 203.62–280.69)	137.92	(– 84.48–360.32)	– 8.63	(– 252.16–234.89)
Pb – Ref.	-	-	-	-	-	-	-	-	-	-
Q2 (0.09 – 0.27)	3.21	(– 4.77–11.21)	– 0.01	(– 13.84–13.82)	2.54	(– 4.71–9.79)	1.01	(– 5.73–7.76)	– 6.74	(– 14.09–0.61)
Q3 (0.28–44)	6.64	(– 0.98–14.27)	– 0.61	(– 13.64–12.42)	2.22	(– 4.72–9.16)	1.07	(– 5.38–7.53)	– 3.99	(– 11.08–3.09)
Q4 (> 0.45)	– 3.28	(– 10.31–3.73)	3.32	(– 10.14–16.78)	1.28	(– 5.04–7.61)	– 2.01	(– 7.89–3.87)	– 2.25	(– 8.71–4.21)
Model 2	-	-	-	-	-	-	-	-	-	-
Pb × Diag.	– 14.06	(– 70.94–42.81)	– 35.56	(– 145.61–74.48)	– 16.93	(– 68.41–34.55)	8.36	(– 39.57–56.29)	– 22.35	(– 74.07–29.36)
As – Ref.	–	–	–	–	–	–	–	–	–	–
Q2 (8.55–17.27)	2.06	(– 5.44–9.56)	6.72	(– 1.06–14.51)	– 2.08	(– 8.55–4.38)	1.60	(– 4.62–7.83)	4.01	(– 2.73–10.75)
Q3 (17.28–37.33)	4.17	(– 3.42–11.76)	– 4.25	(– 14.40–5.89)	0.99	(– 5.63–7.62)	2.42	(– 3.97–8.80)	– 0.74	(– 7.55–6.08)
Q4 (> 37.34)	**8.19***	**(0.34–16.05)**	10.99	(– 0.28–22.26)	**7.98***	**(1.22–14.74)**	0.51	(– 6.00–7.02)	4.03	(– 3.09–11.16)
Model 2	-	-	-	-	-	-	-	-	-	-
As × Diag.	1.71	(– 9.92–13.37)	– 14.87	(– 39.28–9.54)	2.11	(– 7.92–12.15)	2.00	(– 7.67–11.67)	2.83	(– 7.96–13.62)
Hg – Ref.	-	-	-	-	-	-	-	-	-	-
Q2 (0.17–0.32)	1.21	(– 6.40–8.83)	– 3.02	(– 12.79–6.74)	1.40	(– 5.36–8.15)	1.36	(– 4.93–7.65)	– 2.20	(– 9.10–4.69)
Q3 (0.33–0.61)	1.95	(– 5.52–9.43)	1.15	(– 8.24–10.55)	0.95	(– 5.59–7.50)	2.91	(– 3.18–9.00)	– 3.65	(– 10.34–3.04)
Q4 (> 0.62)	– 2.13	(– 10.05–5.80)	– 2.44	(– 13.47–8.60)	1.96	(– 5.03–8.94)	1.85	(– 4.65–8.35)	– 5.06	(– 12.16–2.04)
Model 2	-	-	-	-	-	-	-	-	-	-
Hg × Diag.	**– 45.79***	**(– 87.55 – (– 4.04))**	– 6.31	(– 68.95–56.33)	– 14.12	(– 51.33–23.08)	– 28.45	(– 62.82–5.91)	– 0.33	(– 37.85–37.19)
Cu – Ref.	-	-	-	-	-	-	-	-	-	-
Q2 (3.34–5.33)	– 1.24	(– 8.78–6.29)	– 6.29	(– 22.86–10.28)	– 0.77	(– 7.44–2.90)	2.76	(– 3.41–8.93)	– 2.42	(– 9.10–4.25)
Q3 (5.34–7.92)	– 4.39	(– 11.94–3.15)	– 3.79	(– 18.34–10.75)	– 3.37	(– 9.98–3.23)	– 0.44	(– 6.55–5.66)	**– 6.75***	**(– 13.42 – (– 0.08))**
Q4 (> 7.93)	– 3.22	(– 11.44–5.01)	– 5.71	(– 20.31–8.88)	– 2.18	(– 9.42–5.06)	– 3.88	(– 10.58–2.81)	– 4.93	(– 12.19–2.33)
Model 2	-	-	-	-	-	-	-	-	-	-
Cu × Diag.	8.81	(– 11.55–29.17)	**– 45.86***	**(– 88.27–(– 3.45))**	7.79	(– 10.03–25.61)	7.39	(– 9.08–23.87)	– 15.08	(– 32.85–2.67)

Table 3. Adjusted multiple linear regression model between Wechsler intelligence Scale – IV/V and urinary metals. Q2, Q3, Q4 = second, third, fourth quartile. Q1 – first quartile used as a reference. *$p < 0.05$. Multiple linear regression models: Model 1: adjusted for sex, age, BMI, SDQI, SES and ADHD Diagnosis. Model 2: interaction between metal and ADHD diagnosis. VCI – verbal comprehension index, VSI – visual spatial index, PRI/FRI – perceptual/fluid reasoning index, WMI – working memory index, PSI – speed processing index, Cd - cadmium, Pb - lead, As – arsenic, Hg – mercury, Cu – copper

learning and behaviour[42,43]. Furthermore, even small amounts of Pb are considered toxic and have been linked to ADHD symptoms in children[8,11]. Similarly,studies from Taiwan using the SNAP-IV scale (Swanson, Nolan, and Pelham–IV scale) found an association between Pb exposure and ADHD symptoms, such as impulsivity and inattention[2,6]. However, it is important to note that while Pb is toxic, it can also be asymptomatic at low levels, making it difficult to detect and establish a safe concentration[44]. This challenge was also observed in our study, where the association between Pb exposure and ADHD symptoms appeared even at lower exposure levels (e.g., the second quartile). Therefore, these results should be interpreted with caution, highlighting the need for further research to explore this relationship more comprehensively.

Regarding Cd, our study did not observe any association with any of the subscales of WISC-IV/V and CPT-2/3. This is consistent with earlier studies that also found no association between Cd levels in urine or blood and ADHD symptoms[45,46]. However, other researchers have shown an association between Cd exposure and learning disabilities[22]. Additionally, some studies report an inverse association between Cd levels and verbal comprehension and IQ[6,47,48]. Notably, Rodriguez-Barranco et al. (2014)[48] found that higher Cd levels in urine negatively affected the perceptual reasoning, particularly in boys. The research on Cd's effects remains limited and often presents conflicting results. Given that Cd is classified as a toxic element by the WHO, more comprehensive and focused studies are needed to fully understand its impact on children's neuropsychological development.

Cu is essential for biological growth, but when present in excess, it can cross the blood-brain barrier and induce oxidative stress in neuronal cells. This can be detrimental to cognitive functions and increase the risk of ADHD. Our study supports this by demonstrating that elevated Cu levels are associated with impaired processing speed and higher omission errors in ADHD children, suggesting a link to inattentiveness. Similar

	DET		OMI		COMI		HRT		HRT-SD	
Metals	***β***	***95% CI***	***β***	***95% CI***	***β***	***95% CI***	***β***	***95% CI***	***β***	***95% CI***
Cd – Ref.	-	-	-	-	-	-	-	-	-	-
Q2 (0.04 – 0.05)	– 0.86	(– 4.62–2.89)	1.77	(– 4.01–7.57)	– 1.50	(– 5.18–2.18)	1.80	(– 2.80–6.41)	– 2.94	(– 8.15–2.27)
Q3 (0.05 – 0.07)	0.32	(– 3.54–4.18)	0.98	(– 4.96–6.93)	– 0.97	(– 4.75–2.82)	1.34	(– 3.38–6.07)	– 2.76	(– 7.63–3.08)
Q4 (> 0.08)	– 0.76	(– 4.74–3.22)	1.96	(– 4.16–8.08)	– 1.83	(– 5.73–2.07)	1.90	(– 2.97–6.77)	– 1.25	(– 6.77–4.26)
Model 2	-	-	-	-	-	-	-	-	-	-
Cd × Diag.	– 0.95	(– 124.55–122.65)	– 75.33	(– 265.25–114.59)	– 7.68	(– 128.81–113.44)	36.78	(– 114.46–188.03)	– 51.95	(– 223.14–119.23)
Pb – Ref.	-	-	-	-	-	-	-	-	-	-
Q2 (0.09 – 0.27)	– 1.08	(– 5.14–2.99)	– 3.55	(– 9.80–2.68)	0.89	(– 3.09–4.88)	0.90	(– 4.06–5.87)	– 2.11	(– 7.75–3.54)
Q3 (0.28–44)	– 1.91	(– 5.76–1.95)	– 2.10	(– 8.02–3.81)	– 1.46	(– 5.24–2.32)	3.45	(– 1.25–8.17)	– 1.87	(– 7.22–3.48)
Q4 (> 0.45)	– 1.61	(– 5.26–2.04)	– 3.55	(– 9.15–2.05)	0.05	(– 3.53–3.62)	1.24	(– 3.22–5.69)	– 3.41	(– 8.47–1.65)
Model 2	-	-	-	-	-	-	-	-	-	-
Pb × Diag.	**36.60***	**(9.92–63.29)**	12.53	(– 29.39–54.46)	**40.91***	**(14.93–66.88)**	– 4.22	(– 37.60–29.15)	11.82	(– 26.06–49.70)
As – Ref.	-	-	-	-	-	-	-	-	-	-
Q2 (8.55–17.27)	1.59	(– 2.23–5.40)	– 1.62	(– 7.49–4.25)	2.03	(– 1.71–5.76)	– 1.86	(– 6.53–2.81)	1.07	(– 4.22–6.35)
Q3 (17.28–37.33)	0.19	(– 3.64–4.03)	– 1.95	(– 7.86–3.95)	1.38	(– 2.37–5.14)	– 2.35	(– 7.05–2.35)	0.15	(– 5.16–5.46)
Q4 (> 37.34)	0.65	(– 3.22–4.52)	0.47	(– 5.48–6.44)	0.74	(– 3.05–4.54)	– 1.60	(– 6.35–3.14)	3.37	(– 1.99–8.74)
Model 2	-	-	-	-	-	-	-	-	-	-
As × Diag.	3.73	(– 1.66–9.13)	5.37	(– 2.94–13.67)	2.22	(– 3.08–7.53)	– 0.45	(– 7.09–6.20)	6.46	(– 0.98–13.91)
Hg – Ref.		-		-		-		-		-
Q2 (0.17–0.32)	3.35	(– 0.38–7.09)	– 0.22	(– 6.03–5.59)	**5.08***	**(1.43–8.73)**	**– 5.55***	**(– 10.13 – (– 0.99))**	0.96	(– 4.28–6.21)
Q3 (0.33–0.61)	**3.64***	**(0.08–7.20)**	1.94	(– 3.58–7.47)	2.48	(– 0.98–5.96)	0.10	(– 4.24–4.45)	4.86	(– 0.13–9.85)
Q4 (> 0.62)	**4.77***	**(1.07–8.48)**	5.32	(– 0.44–11.08)	4.22	(0.59–7.84)	– 0.06	(– 4.59–4.46)	3.25	(– 1.95–8.46)
Model 2	-	-	-	-	-	-	-	-	-	-
Hg × Diag.	– 9.95	(– 28.27–8.37)	– 4.67	(– 33.25–23.91)	19.82	(– 37.49 – (– 2.15))	19.53	(– 2.72–41.77)	– 3.15	(– 28.96–22.66)
Cu – Ref.	-	-	-	-	-	-	-	-	-	-
Q2 (3.34–5.33)	– 0.67	(– 4.44–3.11)	– 2.26	(– 7.96–3.44)	0.66	(– 2.99–4.32)	– 2.97	(– 7.36–1.42)	– 3.81	(– 8.96–1.35)
Q3 (5.34–7.92)	– 0.22	(– 4.12–3.68)	5.15	(– 0.74–11.03)	– 3.01	(– 6.78–0.77)	6.27	(1.74–10.82)	2.15	(– 3.17–7.47)
Q4 (> 7.93)	– 0.33	(– 4.45–3.79)	1.61	(– 4.61–7.84)	– 1.67	(– 5.66–2.32)	0.62	(– 4.18–5.41)	– 2.42	(– 8.05–3.20)
Model 2	-	-	-	-	-	-	-	-	-	-
Cu × Diag.	2.58	(– 7.84–12.99)	5.11	(– 10.61–20.82)	– 1.57	(– 11.66–8.52)	10.38	(– 1.63–22.40)	7.77	(– 6.40–21.95)

Table 4. Adjusted multiple linear regression model between continuous performance Test – 2/3 and urinary metals. Q2, Q3, Q4 = second, third, fourth quartile. Q1 – first quartile used as a reference. *$p < 0.05$. Multiple linear regression models: Model 1: adjusted for sex, age, BMI, SDQI, SES and ADHD Diagnosis. Model 2: interaction between metal and ADHD diagnosis. Abbreviations: DET – detectability, OMI – omission, COMI – commission, HRT – reaction time, HRT-SD - reaction time standard deviation, Cd - cadmium, Pb - lead, As – arsenic, Hg – mercury, Cu – copper.

findings were observed in other studies, where elevated salivary Cu levels were significantly associated with a higher likelihood of an ADHD diagnosis[8,26]. These results are consistent with previous research by Zhou et al. (2015)[25], which also found that Cu interferes with working memory. However, some studies have reported decreased Cu levels in ADHD children or found no significant association with Cu serum levels[49,50]. Despite these mixed findings, our data on Cu and neuropsychological performance are innovative and warrant careful review and further validation.

A positive association was observed between As levels and both verbal comprehension in ADHD children and perceptual reasoning in the overall sample, as measured by the WISC-IV/V test. Typically, an inverse association would be expected, since As is considered a toxic metal[2,51]. Studies conducted in regions with high concentrations of naturally occurring As in drinking water have documented its negative effects on the neuropsychological development of children at the ages of 4 and 10 years[52–54]. Most of these studies have examined inorganic As, the more toxic form[55,56]. However, our study participants are from a Mediterranean region (the provinces of Tarragona and Barcelona), an area known for substantial seafood consumption[57,58]. Seafood is a primary dietary source of As, but most of the As found in fish and shellfish is in the form of arsenobetaine, an organic As compound referred to as "fish arsenic", which is considered far less harmful than the inorganic form of As[4]. In addition, seafoods are rich in Omega-3 fatty acids, which are not only beneficial for children's neurodevelopment but also could help counteract the potential toxic effects of the inorganic form of As present in seafood[58,59]. Importantly, we could not differentiate between inorganic and organic As species in our urine analyses, which limits our ability to interpret the health implications of total As levels. Furthermore, while the dietary questionnaire covered general eating habits, it did not include a detailed record of seafood intake, which is a key source of organic As. These findings underscore the need for future research that includes

As speciation and detailed dietary assessments to clarify the distinct neurodevelopmental effects of organic versus inorganic As exposure in children.

Regarding Hg, we found an association with higher detectability and commission errors, and slower HRT on the Conners CPT-2/3 across the entire sample. These results indicate a relation between Hg and inattentiveness. Additionally, in ADHD children, higher omission errors were associated with elevated Hg levels, further supporting the connection to attention problems. These results imply that Hg exposure may negatively impact children's neuropsychological development. Similar associations have been reported in previous studies, linking Hg exposure to hyperactivity, impulsivity, and other ADHD-related symptoms[6,60]. Prenatal Hg exposure is also known to adversely affect neuropsychological development at six months of age and increase the risk of ADHD in children[61,62]. However, the postnatal effects of Hg on children's neuropsychological development have been less explored, highlighting the need for careful consideration of our study's findings and further research in this area.

Strengths and limitations

One of the main strengths of the present study is that it examines the association between heavy metals and neuropsychological performance in children, considering the presence of an ADHD diagnosis (made by DSM-5 criteria through standardised instruments). Furthermore, this study is among the first to explore the association between urine toxic metals and neuropsychological outcomes of children from North-East Spain. These pioneering data not only provide valuable insights into potential environmental influences on neurodevelopment but also contribute to the broader understanding of ADHD's aetiology in a specific regional context. Despite its numerous strengths, the study has several limitations. Firstly, the analysis of metals was conducted using urine samples. While this method is non-invasive, comfortable to pick up and effective for measuring recent exposure to most metals, these substances generally have a short biological half-life in urine, which means they do not remain in the body for long periods. This limits the ability to assess long-term exposure, except for Cd. Cd is unique because of its accumulation in the body over time, making urine levels a reliable indicator of lifetime exposure[4]. Also, the excretion of metals through the urine may vary among individuals secondary to factors such as their diet or kidney function. To mitigate the effect of these factors, we controlled the quality of the diet in the analyses of regression and heavy metal concentrations were adjusted to comparable creatine levels (mg/dL) to minimise variation in urine dilution. Importantly, As can exist in both inorganic and organic forms, which differ significantly in their toxicity. However, our analysis was based on total urinary As and did not distinguish between these forms. Secondly, the study's cross-sectional design limits our ability to establish causality. While we can identify potential associations between heavy metal exposure and neuropsychological outcomes, we cannot determine whether these factors cause the observed effects. Third, the study did not account for additional confounding variables, such as exposure to second-hand smoke or other toxicants could also impact neurodevelopmental health[63,64]. Nevertheless, future studies would benefit from incorporating additional biomarkers, such as blood and hair, which can reflect longer-term exposure to specific metals. This approach, especially when combined with longitudinal study designs, would allow for a more comprehensive and temporally sensitive assessment of exposure patterns and their potential effects on neurodevelopment.

Conclusion

Our study provides evidence on the potential association between postnatal exposure to specific heavy metals and cognitive performance in children, both with and without ADHD, in two regions of Spain. By analysing urine concentrations of heavy metals and their relationship with standardised neuropsychological test outcomes (WISC-IV/V and CPT-2/3), we identified that higher levels of Cu and Hg are potentially associated with poorer cognitive performance across the whole sample. In ADHD children, elevated levels of Cu and Pb were associated with more pronounced cognitive impairments, including reduced processing speed and more frequent attentional errors. These findings suggest that exposure to certain heavy metals may contribute to the severity of cognitive deficits in ADHD children and may even play a role in their neuropsychological development. Overall, this study highlights the importance of monitoring environmental exposures in vulnerable paediatric populations and reinforces the need for public health policies aimed at reducing heavy metal exposure. It also suggests that Cu and Pb warrant further investigation as potential environmental risk factors in the context of ADHD.

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Author contributions

J.C.: Conception and Design, Data Collection, Methodology, Investigation, Supervision, Funding Acquisition, Writing - Review; S.K.: Formal Analysis, Writing - Original and Editing Draft; P.M.: Data collection ; V.A.: Conception and Design, Supervision, Revision. J.A.: Data collection, Funding Acquisition, Revision.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to J.C.-S.