

INVESTIGATING THE ASSOCIATION BETWEEN HEAVY METALS AND ATTENTION DEFICIT HYPERACTIVITY DISORDER IN CHILDREN: AN EXPLORATORY STUDY

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Sharanpreet Kaur: Writing - Original draft preparation, Formal analysis. **Josefa Canals:** Data collection, Conceptualization, Supervision, Resources, Methodology, Writing - Review & Editing, Funding acquisition. **Paula Morales-Hidalgo:** Data collection, Data Curation, Supervision. **José A. Alda:** Data collection, Review & Editing, Funding acquisition. **Victoria Arija:** Analysis, Review & Editing

Ethical Statement: Participants taking part in the study were from three projects and ethical approval was obtained from their respective research ethics committee: EPINED - ethical approval was obtained from the Reus Sant Joan University Hospital's Ethics Committee (13-10-31/10proj5). PRONED – project was approved by the IISPV drug research committee (Ref.CEIM:030/2017; Registry: ClinicalTrials.gov Identifier: NCT05167110) and MetigenADHD – the study protocol was approved by the Ethics Committee of this Hospital (PIC-50-17). Parents of children were explained about the procedure and consented to take part in the study.

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Abstract

Exposure to heavy metals has been associated with affecting children's neurodevelopment, particularly increasing the risk of developing attention-deficit hyperactivity disorder (ADHD). The current exploratory study aims to investigate potential associations between presence of 15 different heavy metals in urine and ADHD. A total of 190 urine samples of participants from clinical and non-clinical population (non-ADHD = 66; ADHD = 124) aged between 6-15 years from Barcelona and Tarragona (Spain) were analysed. Logistic regressions adjusted by sex, age, SES, BMI and diet quality were performed. Highest quartiles (3rd and 4th) of Pb (lead) [aOR 5.33; CI: 1.89- 14.98], Cd (cadmium) [aOR 3.69, CI: 1.38- 9.83], Cu (copper) [aOR 16.46, CI: 4.66, 58.14] and Sb (antimony) [aOR 3.04, CI: 1.12 – 8.23] were significantly associated with increased odds of ADHD DSM-5 diagnosis. Additionally, Cu and Cd were associated with higher scores of inattention symptoms. Whereas, Cu and Sb were associated with hyperactivity-impulsivity severity. This exploratory study provides preliminary valuable evidence, suggesting potential associations between environmental factors, such as metal exposure, with ADHD in school-aged children. These findings highlight the importance of further research to support these associations and, if confirmed, explore strategies to mitigate the potential impacts of these toxicants on children's health.

Keywords- Heavy metals, ADHD, Neurodevelopment, School-Age Children

Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the early-onset chronic neurodevelopmental disorders (NDDs). ADHD is defined as a persistent pattern of inattention and/or hyperactivity–impulsivity that interferes with cognitive and behavioural functioning (APA, 2013). The estimated prevalence worldwide has increased in recent years, ranging from 3.6% and 7.6%, while the estimated prevalence in the province of Tarragona, Spain, stands at 5.5% (Salari et al., 2023; Canals Sans et al., 2021). Although ADHD is highly heritable, different environmental factors also play a determinant role in their etiopathogenesis, particularly during an early development. Among these factors, exposure to toxicants and specifically heavy metals has gained significant attention. While the prenatal period is considered to be the period of utmost vulnerability for ADHD, first three years of life have also been found to be susceptible windows at postnatal level on ADHD symptoms (Lozano et al., 2023). According to WHO (2007) heavy metals exposure is a rising concern for the public health since they can have detrimental for the overall health. Exposure to heavy metals can happen through contaminated food, water, soil, air pollution and surroundings. In particular, children's lower capacity to detoxify and immature metabolic pathways makes them predominantly vulnerable to eliminate toxic chemicals from their bodies (Ghassabian et al., 2018; Spungen, 2019). Since metals are naturally occurring elements, they can be beneficial as well as toxic for the development of children's brain. Heavy metals such as arsenic (As), lead (Pb), mercury (Hg) and cadmium (Cd) are most common air pollutants which can also be found in food and soil. According to the Agency for Toxic Substances and Disease Registry (ATSDR) toxic metals can be harmful to the human brain potentially impacting cognitive functioning of children (WHO, 2007; Vahter et al., 2020; Liu et al., 2019; ATSDR, 2023). Heavy metals such as Pb, Cd, Hg, Sb, and As are listed as priority substances by the ATSDR due to their toxic nature. In contrast, Co, Zn, Se, Mg, Mn and Mo metals are considered essential for human health. Metals such as Cu,

Cr, Ni, and V can play a dual role i.e., essential at low levels but can be toxic at higher concentrations.

Research on exposure to heavy or essential metals demonstrate their significant role in the development of ADHD in children, however with variations in previous studies results likely stemming from methodological heterogeneity and the complexity of the disorder (Robberecht et al., 2020). Studies conducted on heavy metals exposure such as Pb, As and Hg, showed an association between the metals and ADHD in children (Goodlad et al., 2013; Muñoz et al., 2020; Wasserman et al., 2007; Yoshimasu et al., 2014). Similarly, Pb, Cd and Sb were associated with susceptibility to ADHD and symptom severity in school-age children (Lee et al., 2018). In particular Pb is a well known neurotoxic playing a major role in the development of ADHD in children, even if present in small amounts can be harmful to children's cognitive functioning development as well as known to diminish functions of all body organs (ATSDR, 2023; He et al., 2019). Even though As is a toxic substance but its relation with ADHD has been found inconsistent such as a study conducted by Muñoz et al., (2020) found an association of As with ADHD in children only in the fifth quintile i.e., above 31.1 µg. Furthermore, a prenatal exposure to As and ADHD development risk in children found a negative relation between the two factors (Skogheim et al., 2021). A study conducted by Hawari et al., (2020) showed that ratio of Pb increase and manganese (Mn) decreases play a vital role in ASD and ADHD or co-occurrence of both the disorders in children to develop. Although, Mn is an essential element for the development of cognitive function however if inhaled and exposed to manganese in excess demonstrate to be toxic affecting cognitive functioning such as contributing in developing ADHD children (Rodríguez-Barranco et al., 2013). Additionally, some metals such as Co, Ni, Cu, Sn and Mo are found to increase oxidative stress leading to lipid and DNA damage, hence, suggesting an association with risk to ADHD development (Li et al., 2020).

Studies suggest significant differences in the effects of metals based on sex, such as their association with disparities in neuropsychological development between boys and girls (Caparros-Gonzalez et al., 2019; Lozano et al., 2023). Furthermore Hashemi et al., (2023) found notable differences in metal concentrations between boys across different age groups and a significant association between urinary As and BMI. Additionally, it has been observed that children with ADHD were found positively associated with unhealthy diet such as high consumption of red and processed meat, savoury cereals, sweets, dairy desserts, sodas (Rojo-Marticella et al., 2022). It is important to acknowledge, however, that certain foods, rich in omega-3 and iron, known for their neurodevelopmental benefits, might potentially counteract the effects of some metals (Fuentes-Albero et al., 2019; McCann et al., 2020). Therefore, it is essential to keep these factors in consideration while working on metals and ADHD in children.

Despite a growing interest in exploring factors contributing towards the development of ADHD in children there is still a significant gap to better understand heavy or essential metal's role with the disorder. Previous studies have explored an association between heavy metals and ADHD, however there is a lack of comprehensive research that considers wide range of different heavy and essential metals and diagnosis of ADHD with their presentation's severity (inattention and hyperactivity-impulsivity) in children. Therefore, current exploratory study aims to examine potential associations between 15 different metals such as Lead (Pb), arsenic (As), mercury (Hg), cadmium (Cd), chromium (Cr), copper (Cu), cobalt (Co), antimony (Sb), zinc (Zn), selenium (Se), magnesium (Mg), vanadium (V), manganese (Mn), nickel (Ni) and molybdenum (Mo) and the presence of ADHD in children, further taking into account ADHD presentations. We aim to explore individual effect and identify levels at which of each of the metals show an effect after adjusting for sociodemographic and nutritional covariates.

Methods

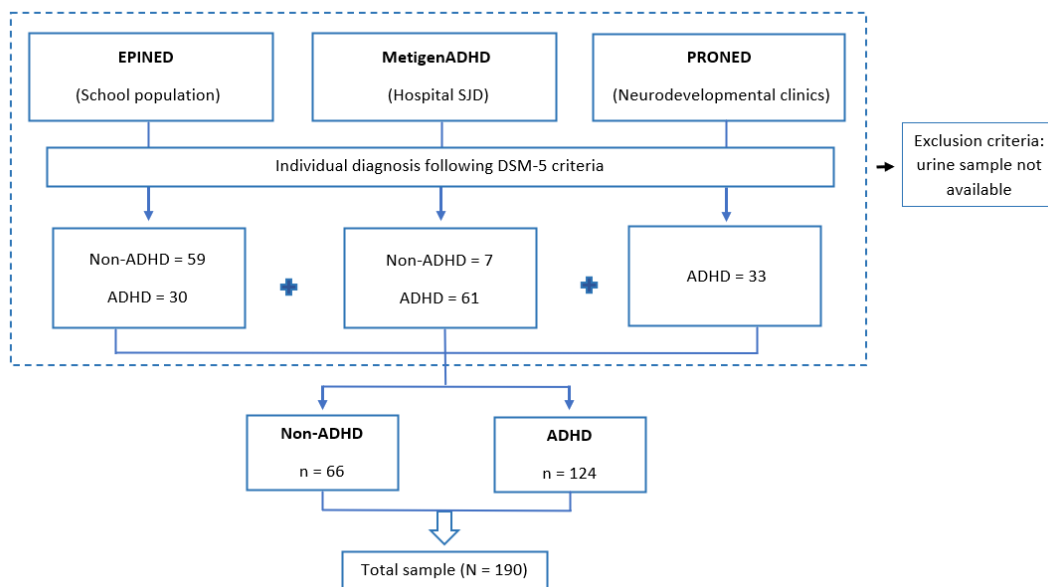
2.1 Participants and diagnosis procedure

A total of 190 children urine sample aged between 6 – 15 years residents in two Spanish provinces (Barcelona and Tarragona) were collected for the current study. These children were divided into two groups such as 124 with ADHD and 66 were non-ADHD (without diagnosis of other NDDs such as autism) (Fig. 1). The diagnosis was conducted by psychiatrists and psychologists following the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders 5th Edition) criteria. ADHD was assessed using Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997). Parents further answered Spanish version of the Conners 3rd Edition–Parent Short Form (Conners, 2008) used to collect symptoms of inattention and hyperactivity-impulsivity, apart from other associated characteristics to the ADHD. Parents were explained about the procedure and consented to take part in the study. Intellectual quotient (IQ) of the children was assessed using the Wechsler Intelligence Scales for Children (WISC-V or WISC-V)(Wechsler, 2005, 2014).

Participants taking part were from the following projects: EPINED, PRONED and MetigenADHD. Ethical approval was obtained from respective research ethics committees. EPINED (Epidemiological Research Project on Neurodevelopmental Disorders) is a double-phase cross-sectional study carried out data collection from years 2015 - 2022 from schools in the province of Tarragona (Spain). A detailed procedure of ADHD assessment protocols has been previously described in Canals Sans et al. (2021). The urine sample of children was from those taking part in the second phase of the study between 2017-2021 years corresponding to the individual assessment of the child and families. PRONED (Nutritional intervention in children with ASD and/or ADHD: randomized controlled trial with probiotics) is a controlled, double-blinded, randomised trial with dietary supplements conducted between 2019-2021. The sample obtained was from the pre-intervention phase of the project and children visiting

neurodevelopmental specialised clinics in the province of Tarragona (Spain). MetigenADHD (Metagenomic and metabolomic profiles in children and adolescents with ADHD) is an observational study carried out between years 2017 - 2019 from Barcelona (Spain) with children who were assessed and diagnosed with ADHD by the service of child psychiatry of the Hospital Sant Joan de Déu (HSJD). We employed probability sampling to recruit participants, ensuring that every member of the target population had an equal chance of being selected. This approach enhances the representativeness and external validity of our sample. Additionally, the studies were conducted following the same protocol for data collection and by the same researchers, ensuring consistency and reliability across all studies.

Fig. 1: Flow chart of participants recruitment



2.2 Urine samples collection and preparation

Parents collected the urine sample of the children fasting early morning in a 12 ml transparent polystyrene tube and stored in refrigerator until the delivery. To reduce the risk of exogenous contamination, guidelines were provided to parents on how to collect the urine sample.

Collected samples were centrifuged at 600g for 10 min at 4 °C in the research laboratory. The

supernatant was transferred into 1 ml sterile screw cap cryotubes and stored at -80 °C until sent to the specialised laboratory for the metals and urine creatinine levels concentration analysis.

2.3 Urinary metal screening: equipment and reagents

To analyse 15 elements such as: Pb, As, Hg, Cd, Cr, Cu, Co, Sb, Zn, Se, Mg, V, Mn, Ni and Mo, the urine samples were diluted 1:10 in ultrapure water (Milli-Q, Merck, Darmstadt, Germany) containing 2% HNO₃ (Nitric acid; Merck, Darmstadt, Germany) and 1% HCl (Hydrochloric acid; Merck) using appropriate metal standard solutions (Agilent Technologies, Santa Clara, CA, USA). The multielement analyses were performed on an Agilent 8900 triple quadrupole ICP mass spectrometer (ICP-MS; Agilent Technologies). Before the analysis, instrument was tuned, and performance parameters were verified. Further, to ensure the quality, a multielement 400 µg/L internal standard solution containing Sc, Ge, Ir, and Rh was added online to the samples (ISC Science, Oviedo, Spain). Additionally, a certified reference material, Seronorm (Sero, Billingstad, Norway) Trace Elements Urine L-1 (reference 210605), along with a blank and an intermediate calibration standard, was reanalysed every 12 samples to maintain the accuracy. The National Institute of Standards and Technology NIST (Gaithersburg, MD, USA) Trace Elements in Natural Water Standard Reference Material SRM 1640a was also used as a certified reference material and analysed at the beginning and end of each sequence. Furthermore, one sample out of every 12 was reanalysed at the conclusion of each session to ensure consistency. The limits of detection (LOD) in units of µg/L for each metal were as follow: Pb – 0.08, As – 0.5, Hg – 0.05, Cd – 0.03, Cr - 0.2, Cu - 0.9, Co - 0.005, Sb - 0.03, Zn - 4, Se -1, Mg - 5, V - 3, Mn - 0.05, Ni - 0.4 and Mo - 0.03. Reagents Sistema ADVIA 1800 Chemistry and Sistema ADVIA 2400 Chemistry (Warren et al., 2014) was used to measure urinary creatine levels. To limit the variation in urine dilution, heavy metals concentrations were adjusted relative to their corresponding creatine levels (mg/dL).

2.4 Covariates

Covariates were entered in the statistical analyses as potential confounders and were selected based on published literature, and the biological plausibility (Bauer et al., 2020; Hashemi et al., 2023; Li et al., 2020; Lozano et al., 2023). Age and sex, and other descriptive data of the sample were collected from sociodemographic questionnaire answered by the parents. Body mass index (BMI) was determined by anthropometric data obtained by a nutritionist, or a nurse when the sample was from Hospital SJD. Furthermore, parents answered Food Consumption Frequency Questionnaire validated in Spanish population (FCFQ; Trinidad Rodríguez et al., 2008) which provided the Diet Quality Index measure of children (SDQI; Norte Navarro & Ortiz Moncada, 2011). The SDQI is scored on a scale from 0 to 100, with the following cut-off points: ≥ 80 indicates a healthy diet, 50-79 indicates a diet that needs improvement, and ≤ 49 indicates an unhealthy diet.

2.5 Statistical analysis

Statistical analysis was conducted with SPSS IBM version 29. A significance level of $p < 0.05$ was accepted. In case quantitative variables i.e., BMI, SDQI and age are expressed as mean $\pm$ SD, whereas for categorical variables such as sex, socio-economic status (SES), ethnicity and area are presented as percentage (%). A t-test for independent samples was conducted to observe the differences in heavy metals by area i.e., Tarragona vs Barcelona. A Shapiro-Wilk test was conducted to check for normality which showed data was non-parametric. Therefore, appropriate tests were used.

Kruskal-Wallis test was conducted to analyse the continuous variables and the significant difference in heavy metal concentrations between groups as well as presentations of ADHD such as inattentive and combined (including 3 participants presenting hyperactivity-impulsivity presentation). Further, significant heavy metal concentrations were stratified into quartiles. However, due to values close to zero, V was stratified into <90 and >90 percentiles whereas

Mn was stratified into <50, 75-50, >75 percentiles. Logistic regressions were performed to analyse the relationship between metals (stratified into quartiles or percentiles) and ADHD (vs non-ADHD), adjusted by covariates: sex (male=0, female=1), age (years), BMI (Kg/m²), SDQI score (diet), SES (socio-economic status) of the family including the interaction between sex and each metal (sex*metal), using first quartile as a reference. In the results of this model, the interaction was not significant. Therefore, the logistic regression analysis was carried out eliminating the interaction variable. Additionally, a multiple linear regression was conducted to analyse the metals association with ADHD presentation for inattention and hyperactive-impulsive symptoms from log transformed Conners test score. Given the exploratory nature of the study, no adjustments were made for multiple comparisons.

Results

3.1 Sample demographics and metals distribution

Sociodemographic details of children non-ADHD vs ADHD can be found in Table 1. The mean age of the total sample was 10 (SD = 1.85; ranging 6 – 15 years). Overall, there is a higher number of males (71.6%) than females (28.4%), but this preponderance for male sex was in ADHD (77.4%). Majority of children were from Spain (92.39%) and from families with medium level of SES (72.99%) with mostly residing in the province of Tarragona (64.21%). Nevertheless, the children diagnosed with ADHD proceeded in similar number from Barcelona (49.2%) and Tarragona (50.8%). The BMI did not differ between groups and the diet quality was slightly higher in non-ADHD than ADHD children, although all the population is within the “needs improvement” range. The intelligence quotient of children ranged between minimum of 63 and maximum of 155 with 2.1% of children < or equal 70 and 20.5 % > or equal 120.

Table 1: Sociodemographic characteristics of non-ADHD and ADHD children.

Variables		N	Non-ADHD (66)	ADHD (124)	p
			n (%)	n (%)	
Sex	Male	131	35 (53.0)	96 (77.4)	<.001*
	Female	59	31 (47.0)	28 (22.6)	
Ethnicity	Spain	170	60 (90.9)	110 (93.2)	0.571*
SES	Low	10	2 (3.2)	8 (7.1)	0.228*
	Medium	127	43 (69.4)	84 (75.0)	
	High	37	17 (27.4)	20 (17.9)	
Area	Tarragona	122	59 (89.4)	63 (50.8)	<.001*
	Barcelona	68	7 (10.6)	61 (49.2)	
			M ± SD	M ± SD	
Age	(years)	232	10.48 ± 1.07	10.27 ± 2.15	.553**
BMI	(kg/cm)	232	19.05 ± 3.70	19.26 ± 3.46	.591**
SDQI		232	62.92 ± 7.01	61.74 ± 6.04	.094**
IQ		189	110.77 ± 14.37	104.77 ± 17.64	.013**

Abbreviations: SES: socio economic status; BMI: body mass index; SDQI: Spanish diet quality index, IQ: Intelligence quotient

*Chi squared; **Mann U Whitney U test.

The heavy metals levels distribution in the sample by area (Tarragona and Barcelona) can be found in supplementary materials, Table S1. Metals such as V ($p = <.001$), Cr ($p = .002$), Mn ($p = <.001$), Sb ($p = .004$) and As ($p = <.001$) were significantly higher in the sample of province of Tarragona than those of Barcelona. In contrast, Cd was higher in Barcelona than in Tarragona ($p = .005$). Spearman correlation show a moderate range (0.35 – 0.55) correlation between Pb, Cd and Cu, whereas V and As show weak (0.14) correlation between them (S.Fig 1 – supplementary material).

Table 2 provides a further analysis of all metals and comparison between groups (non-ADHD and ADHD). Significant difference between non-ADHD group and ADHD (both inattentive and combined presentations) is seen for Pb, V, Cr, Cu, and Cd. A higher mean of Pb, Cd, Cu, and Sb is observed in ADHD than non-ADHD, but for Sb difference was found in combined ADHD. As

was significantly higher in non-ADHD than in inattentive ADHD. No difference between the ADHD presentation (inattention and combined) is shown.

Table 2: Association between exposure to heavy metals detected from urine samples and comparison between groups: non-ADHD and ADHD.

Metals (µg/l)	Non-ADHD ^a (N = 66)	ADHD			<i>p</i> ^{ab}	<i>p</i> ^{acd}
		Total ^b (N = 124)	ADHD presentations Inattentive ^c (N = 44)	Combined ^d (N = 80)		
Pb	.18 ± .30	.32 ± .28	.33 ± .30	.31 ± .26	.007	ac, ad**
V	.00 ± .70	.00 ± .08	.00 ± .57	.00 ± .05	<.001	ac, ad***
Cr	.35 ± .24	.26 ± .45	.24 ± .37	.28 ± .55	<.001	ac, ad***
Mn	.04 ± .09	.02 ± .28	.03 ± .18	.04 ± .33	.428	
Cd	.04 ± .05	.06 ± .05	.05 ± .05	.06 ± .05	.006	ac, ad**
Sb	.02 ± .09	.03 ± .19	.02 ± .17	.04 ± .19	.011	ad**
Hg	.35 ± .41	.33 ± .52	.27 ± .49	.37 ± .53	.220	
Co	.40 ± 1.23	.41 ± .40	.37 ± .53	.42 ± .40	.498	
Cu	3.92 ± 3.99	6.57 ± 3.64	5.84 ± 3.21	6.71 ± 4.09	<.001	ac, ad***
Ni	2.47 ± 2.08	2.47 ± 4.85	2.46 ± 1.24	2.49 ± 5.77	.904	
Mo	43.97 ± 31.21	49.05 ± 36.60	48.49 ± 27.81	49.93 ± 39.59	.624	
Se	30.78 ± 14.20	35.56 ± 16.42	35.23 ± 12.07	34.19 ± 17.95	.602	
As	20.41 ± 56.12	13.05 ± 71.26	10.09 ± 43.84	15.08 ± 82.27	.006	ac**
Zn	408.50 ± 325.19	428.88 ± 261.24	427.57 ± 170.36	432.89 ± 300.55	.517	
Mg	11.52 ± 3.05 (x 10 ⁴)	10.23 ± 4.64 (x 10 ⁴)	9.47 ± 3.88 (x 10 ⁴)	10.31 ± 4.90 (x 10 ⁴)	.204	

Metals Values are presented as Median ± SD.

P(ab): group differences (non-ADHD and ADHD). P(acd): ADHD presentation differences

ADHD presentation Kruskal-Wallis differences: **p* < .05, ***p* < .01, ****p* < .001.

Abbreviations: Pb: lead; V: vanadium; Cr: chromium; Mn: manganese; Cd: cadmium; Sb: antimony; Hg: mercury; Co: cobalt; Cu: copper; Ni: nickel; Mo: molybdenum; Se: selenium; As: arsenic; Zn: zinc; Mg: magnesium.

3.2 ADHD and heavy metals

Non-adjusted and adjusted logistic regressions between significant heavy metals identified in table 2 such as Pb, Cd, As, Cr, Cu, Sb and V for ADHD vs non-ADHD group were made (Table 3).

No significant differences between ADHD inattention and combined presentation were observed, hence, models were performed for presence of ADHD. To measure the multicollinearity of covariates with heavy metals, variance inflation factor (VIF) indicated no correlation between the factors (sex = 1.03, age = 1.11, BMI = 1.14, SDQI = 1.02, SES = 1.09).

Sex was found to be significant in the models therefore an interaction covariate metal*sex was tested which was not significant in any model indicating an independent effect of sex and metals on ADHD. A significant linear positive relation was found between Cu and Cd levels and ADHD. Cu and Cd in the 4th quartile were associated with an elevated risk of ADHD (aOR = 16.46, CI: 4.66- 58.14, $p < .001$; aOR = 3.07, CI: 1.13-8.29, $p = .027$ respectively). Pb and Sb higher levels were associated with ADHD risk, but show a non-linear positive relation higher in the 3rd quartile respectively (aOR = 5.33, CI: 1.89-14.98, $p = .002$; aOR = 3.04, CI: 1.12 – 8.23). In case of As, regression did not provide significant results. On the contrary, for Cr and V (percentile 90) a negative association with ADHD can be observed. However, considering significantly lower levels of these metals (Cr, As, V and Sb) in Barcelona (mean levels very low) than in Tarragona (S1 – supplementary table), we have performed the adjusted regression models separately by area (S2 - supplementary table). In case of Tarragona, a non-significant association was found between Cr or As and ADHD. A significant positive association was found for Sb in the 3rd and 4th quartile in Tarragona area. The only metal that maintained the negative association was V. Graphical representation of the significant adjusted odd ratios can be found in Fig 2. Logistic regressions were also conducted for other metals, including Mn, Hg, Co, Ni, Mo, Se, Zn, and Mg, but these analyses did not yield significant results.

Additionally, to assess the relation between heavy metals and ADHD symptoms severity from Conners test score, we performed adjusted multiple linear regression models for metals with previous significant relation with the disorder. A significant relation was observed for inattention and Cd ($\beta = .053$, $p = .029$, 3rd quartile), Cu ($\beta = .057$, $p = .015$, 2nd quartile) and Pb ($\beta = .068$, $p = .005$, 2nd quartile). For hyperactivity-impulsivity severity significant relation was observed for Cu ($\beta = .059$, $p = .029$, 2nd quartile) and Sb ($\beta = .074$, $p = .011$, 4th quartile). However, V, As and Cr exhibited no significant correlation with ADHD symptom score.

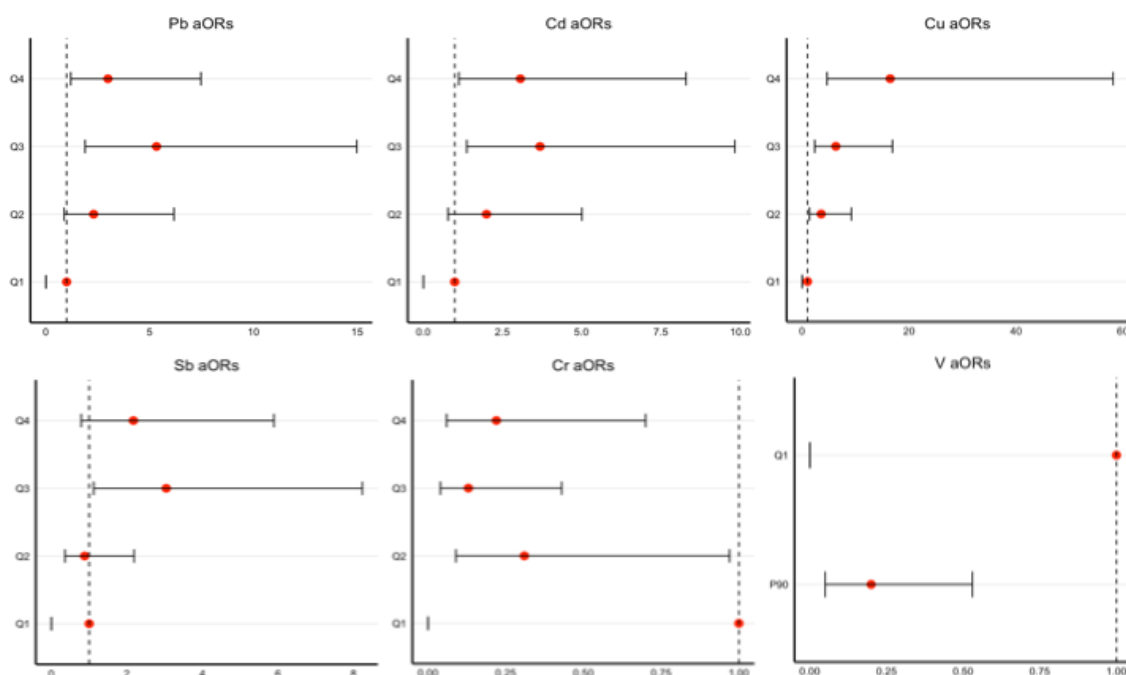
Table 3: Crude and adjusted logistic regression models for ADHD vs non-ADHD group.

		Crude			Adjusted		
		OR (CI 95%) ^a	p ^a	R ^{2a}	aOR (CI 95%) ^b	p ^b	R ^{2b}
Pb	Q1 (<.08)	1.00			1.00		
	Q2 (.09 - .27)	2.46 (1.03 – 5.87)	.044	.095	2.30 (.88 – 6.17)	.089	.230
	Q3 (.28 - .44)	4.66 (1.90 – 11.42)	<.001		5.33 (1.89 – 14.98)	.002	
	Q4 (> .45)	2.92 (1.26 – 6.56)	.010		2.99 (1.20 – 7.47)	.019	
Cd	Q1 (<.03)	1.00			1.00		
	Q2 (.04 - .05)	2.24 (.97 – 5.13)	.057	.064	2.00 (.79 – 5.01)	.139	.212
	Q3 (.05 - .07)	2.75 (1.18 – 6.42)	.019		3.69 (1.38 – 9.83)	.009	
	Q4 (> .08)	3.16 (1.34 – 7.46)	.009		3.07 (1.13 – 8.29)	.027	
As	Q1 (<8.54)	1.00			1.00		
	Q2 (8.55 - 17.27)	.82 (.34 – 2.0)	.668	.040	.74 (.28 – 2.02)	.568	.176
	Q3 (17.28 – 37.33)	.57 (.23 – 1.38)	.034		.52 (.19- 1.40)	.197	
	Q4 (> 37.34)	.39 (.16 - .93)	.034		.41 (.15 – 1.09)	.076	
Cr	Q1 (<.22)	1.00			1.00		
	Q2 (.23 - .31)	.24 (.08 - .67)	.007	.145	.31 (.09 - .97)	.046	.241
	Q3 (.32 - .39)	.13 (.05 - .35)	<.001		.13 (.04 – .43)	<.001	
	Q4 (>.40)	.19 (.07 - .55)	.002		.22 (.06 - .70)	.011	
Cu	Q1 (< 3.33)	1.00			1.00		
	Q2 (3.34 – 5.33)	3.16 (1.38 – 7.25)	.007	.206	3.56 (1.37 – 9.21)	.009	.338
	Q3 (5.34 – 7.92)	4.66 (1.99 – 10.92)	<.001		6.30 (2.35 – 16.89)	<.001	
	Q4 (>7.93)	13.14 (4.42 – 39.09)	<.001		16.46 (4.66 – 58.14)	<.001	
Sb	Q1 (< 0.093)	1.00			1.00		
	Q2 (.094 – .028)	.90 (.41 – 2.00)	.800	.056	.88 (.36 – 2.19)	.797	.208
	Q3 (.029 – .052)	2.49 (1.02 6.05)	.044		3.04 (1.12 – 8.23)	.029	
	Q4 (> .053)	1.97 (.82 – 4.76)	.130		2.17 (.79 – 5.89)	.129	
V*	Q1 (<.01)	1.00			1.00		
	P90 (>.02)	.14 (0.04 – .44)	<.001	.096	.20 (.05 – .53)	.012	.198

a - crude model; b - adjusted model for sex, age, BMI, SES and SDQI. *V divided into 90 percentiles. Quartiles and percentile levels are in µg/l.

Abbreviations: Pb: lead; Cd: cadmium; Cr: chromium; Cu: copper; Sb: antimony; V: vanadium

Fig. 2: Graphical representation of significant models' odd ratios and 95% confidence interval of logistic regression ADHD vs non-ADHD children.



4. Discussion

The current exploratory research examined potential associations between exposure to 15 different, essential and heavy metals with the presence of ADHD (and presentation) in children. Here, we found a positive association of the exposure to heavy metals such as Pb, Cd, Sb and Cu with the ADHD. Notably, Sb is also associated with ADHD in children from Tarragona region, presumably due to higher metal levels. While, V showed a negative relation with the disorder. Nevertheless, we did not find significant differences in metals that should be essentials such as Zn, Mg and Se. Furthermore, contrary to findings by other researchers, we did not observe an interaction between metals and sex concerning ADHD. We observed a correlation in the moderate range between Pb, Cu, and Cd. Whereas V and As show weaker correlation. While this finding suggests a possible interaction between these metals, further research is needed to explore and confirm any potential cumulative effects. Furthermore, based on parental Connors score, we found an association between Cu and Sb with

hyperactivity-impulsivity severity, whereas only Cu, Cd and Pb showed an associated with inattention severity in ADHD. Although some authors previously attempted, our study is one of the first to thoroughly explore potential associations between metals and ADHD presentation. Therefore, this area of research warrants a careful consideration for future studies.

4.1 Lead

Lead is a toxic and omnipresent element however the main source of exposure happens through environment due to anthropogenic emissions, weathered surfaces containing Pb-based paints and corrosive water coming through Pb-pipes which can be a highly localized area for concentration of Pb in water (ATSDR, 2023, Hanna-Attisha et al., 2016). Besides having detrimental effects on the physical health, it is also well-known to affect the neurodevelopmental growth in children (He et al., 2019). As suggested by the European Food Safety Authority (2010), we observed a non-linear association between Pb and ADHD which may not support an association dose – response, suggesting that Pb can be harmful regardless of the exposure level (Vrijheid et al., 2016). Results of the current study are in line with previous studies that found elevated Pb levels present in ADHD children when compared to controls from blood and urine samples (Hawari et al., 2020; Li et al., 2020; Panda & Panda, 2022; Sahu et al., 2023). Besides ADHD, exposure to Pb in children as been found to be associated with reduced IQ, behavioural issues and learning disabilities (Xi & Wu, 2021) and higher level of Pb detected in autistic children (Ding et al., 2023). Additionally, we also observed that Pb is potentially associated with ADHD inattention presentation score, similarly noted by previous research (Lee et al., 2018).

4.2 Cadmium

Cadmium is another well-known toxic heavy metal and its sources can be both natural and anthropogenic (WHO, 2007). Cd is a nonbiodegradable in nature and does not have essential

biological function for our health. However, it incorporates into our food system through its presence in the soil, water and air for which it is known to be a threat to food safety (Suhani et al., 2021; Wang et al., 2023). Specifically, grains and potatoes, spinach and lettuce, soybeans, peanuts and sunflower seeds have high content on Cd, 0.05– 0.12 mg Cd/kg (ATSDR, 2012). In a recent study conducted by Pokharel & Wu (2023) found that children mainly consuming rice, spinach, oats, potatoes, barley and wheat exceed the Cd level suggested by the ATSDR due to which bioaccumulation of Cd hence as result increases oxidative stress. Cd role as a neurotoxicant is complex bringing changes to the central nervous system (CNS) and yet to be further explored (European Food Safety Authority, 2009, Karri et al., 2016). Previous studies on the Cd exposure in children suggest its adverse effects on the cognitive and neuropsychological function for example poor cognition, reduced IQ, risk of learning disabilities and need for special education (Chandravanshi et al., 2021; Ciesielski et al., 2012, 2012; Sanders et al., 2015; Zhou et al., 2020). Furthermore, studies on prenatal Cd and ADHD suggest a significant association between the two factors, suggesting its interference with the brain development (Kim et al., 2020; Masumoto et al., 2022; Skogheim et al., 2021). In continuing the exploration of the role of Cd in neurotoxicity, our study provides further valuable insight on the topic. In the present study, we found a potential association between exposure to Cd and ADHD in children, these results are also in line with previous studies (Nayak et al., 2023). Similarly a study from southern Spain suggested a cognitive delays in boys when exposed to Cd (Rodríguez-Barranco et al., 2014). Additionally, we observed a potential association between Cd and inattention presentation of ADHD being one of the first studies to explore that the results need to be carefully considered for future research.

4.3 Arsenic

Arsenic is another commonly and naturally occurring toxic substance. It is primarily exposure can be through both the digestive tract (food and water) and the respiratory system (poor air

quality). Primary dietary source of As is from seafood, rice or cereals, poultry and mushrooms. Although scientists do not determine the type of arsenic (inorganic or organic) but shellfish and fish are known to be primary source of organic As (ATSDR, 2007). In our study, we did not obtain a significant relation between As and diagnosis of ADHD in children. Previous investigations are primarily focused red on the inorganic As with varying findings. As, in its inorganic form, has been mainly identified as neurotoxin impacting cognition function, IQs, lack of attention or increase impulsivity (Agency for Toxic Substances and Disease Registry (ATSDR), 2023; Rodríguez-Barranco et al., 2016). Muñoz et al., (2020) found a significant association with ADHD solely at the highest level of exposure to inorganic arsenic, however there are studies who found higher As level in autistic children than controls (Ding et al., 2023). Conversely, some studies on prenatal As exposure suggest no association with development of ADHD in children (Forns et al., 2014), whereas others (Skogheim et al., 2021) propose risk of development of ADHD. Notably, primary source of arsenic in province of Tarragona is mainly organic due to higher intake of seafood and rice (Domingo et al., 2012; Martí-Cid et al., 2007). On the other hand, organic arsenic is considered less harmless than inorganic form (Molin et al., 2015) and it is noteworthy that seafood, being a rich source of Omega-3, is not only associated with benefits for children's neural growth (Fuentes-Albero et al., 2019) but may also mitigate the potential any toxic effects of arsenic (Molin et al., 2015). However, there is still need to further investigate the relation of As in ADHD diagnosis in children, taking into account the specific form of arsenic exposure.

4.4 Chromium

Chromium is a naturally-occurring and essential in small amount for the human health. However main source of exposure to chromium is through breathing air containing Cr released from industries (ATSDR, 2012). The role of Cr on neurodevelopment is limited and come from some number of studies who explored the association. In the present study we found lower Cr

levels in ADHD group than non-ADHD, although higher Cr level detected from the sample of province of Tarragona than Barcelona. Additionally, we observed a negative relation with ADHD signifying less chances of developing ADHD in children. These results are in line with previous studies conducted on chromium obtained from hair samples (15%) and serum (21%) found lower in ADHD children than a control group (Perham et al., 2022; Skalny et al., 2020). On the other hand a study conducted by Caparros-Gonzalez et al., (2019) from southern Spain region reported detrimental effect of chromium on neuropsychological development. Cr is known to act as a cofactor for an enzyme responsible for increasing sensitivity to insulin involved with type 2 diabetes demonstrating an increased association with ADHD (Panchal et al., 2017; Landau & Pinhas-Hamiel, 2019). There might be an underlying link of Cr homeostasis and ADHD pathogenesis which needs to further explored. Moreover, our study is one of the first to document negative relation of Cr and ADHD development in children analysed from urine samples, which findings need to be cautiously interpreted.

4.5 Vanadium

In the current study we found that exposure to Vanadium and risk of developing ADHD is less likely to happen. Generally, vanadium can be found in soil, water, food and soil but present in nanogram quantities (ATSDR, 2012; French & Jones, 1993). Even though Vanadium is a metalloid and trace element, it can accumulate in the brain tissue and be potentially involved pathophysiology of neurological disorders (Folarin et al., 2017). Furthermore, its role in essentiality is debatable and yet has not been clear (Panchal et al., 2017). To best to our knowledge there is little to no evidence present in relation to ADHD and exposure to Vanadium. Therefore, results of this study need to be carefully interpreted recommending further research to better understand its mechanism and, if any, potential health benefits.

4.6 Antimony

Exposure to Sb can be through water or soil but its toxic nature is predominant with biological effect such as irritation to eye and skin, harmful to normal functioning of body organs (Centers for Disease Control and Prevention (CDC), 2022; ATSDR, 2019). However, airborne Sb relation to neuropsychological functioning still needs to be established (ATSDR, 2023). In the present study we found Sb being associated with ADHD and most likely from the sample of Tarragona. The metal exposure level from the sample of Barcelona was comparatively lower than Tarragona. Similarly, previously conducted study by Lee et al (2018) found association between Sb and susceptibility to ADHD in school-age children. On the contrary, in sample of Barcelona, Forns et al., (2014) did not find a significant role Sb in neuropsychological development of children specially with ADHD symptoms. However, the limited availability of data on the role of Sb with ADHD in children demands further investigation. Moreover, our study identified a potential association between Sb and the hyperactivity-impulsivity symptoms of ADHD. While Lee et al. (2018) reports similar findings, our study is among the first to explore this association, highlighting the need for further research.

4.7 Copper

Copper is considered an essential element for the biological development but an excessive amount can be detrimental (Bulcke et al., 2017; Kumar et al., 2021). In our study, we observed that as the exposure to copper increases the risk of development of ADHD. Our findings are in line with previous studies who found similar results for ADHD (He et al., 2019; Li et al., 2020; Skalny et al., 2020). Moreover, a study conducted on prenatal exposure to pollutants, although non-monotonic, suggest a relation between copper and risk ADHD in children but did not detect the same association between risk of developing ASD in children and copper (Skogheim et al., 2021). Furthermore, our study is one of the first that explored and observed that the presence of copper is correlated to an increased inattention and hyperactivity-impulsivity

presentations of ADHD. Although, Elbaz et al., (2017) conducted a study on ADHD presentation but did not find any significant relation among the factors. There is limited previous evidence that explored the heavy metals and ADHD presentation in children, therefore, the results need to be interpreted with caution and further research is recommended on the topic.

4.8 Strengths and Limitations

One of the major strengths of the current study was that it explored the association of 15 heavy metals with the presence of diagnoses of ADHD and non-ADHD without neurodevelopmental disorders in school-age children. We have assessed two populations with different levels of heavy metals between them and the results presented have been adjusted with covariates related to nutritional status. Although the study provided good understanding on various metals it comes with some limitations. Firstly, our study assesses cross-sectional association between metals and ADHD, limiting our ability to establish causality or determine whether these metals act as a potential risk factor for development for ADHD. It highlights the necessity for longitudinal studies to better explore the effects of metal exposure during critical windows of neurodevelopment. Additionally, while this study adjusted for essential covariates (sex, age, BMI, SES and diet quality), it could not adjust for other factors known to contribute to ADHD, including genetics, other environmental pollutants such as particulate matter, nitrogen dioxides, sulphur dioxide, pesticides, polycyclic aromatic hydrocarbon (PAH) which are equally considered neurotoxic in nature. Moreover, metals exposure was measured through urine, a non-traditional biomarker, and most metals have short biological life i.e., it only measures exposure to metals in the previous days or hours except for Cd which indicates long term exposure (ATSDR, 2023). Finally, the sample size used in this study is relatively small, which may affect the statistical power and the ability to detect subtle associations. This limitation restricts the generalizability of our findings and suggests the need for further research with larger cohorts to validate and expand upon our results. Therefore, to address

these limitations, future studies should consider alternative methodological approaches, such as longitudinal approaches, multi-pollutant models, and advanced statistical techniques such as environmental risk scores or machine learning, to better control for confounding and assess complex interactions between multiple environmental exposures.

5. Conclusion

The current exploratory study provides a comprehensive information on the potential associations of both heavy and essential metals exposure with neurodevelopmental disorder, in particular, ADHD in school-aged children. Remarkably it detected the exposure to heavy metals such as Pb, Cd, Cu and Sb (Tarragona) potentially associated with the presence of ADHD. Furthermore, Cu and Sb being associated with higher hyperactivity-impulsivity symptoms and Cu, Cd and Pb with inattention severity. Whereas V unveiled a negative correlation with ADHD, suggesting a distinctive pattern of influence. These results highlight the complex interactions between exposure to heavy metals and neurodevelopmental disorders, providing important insights for research to further investigate the relation between these factors to minimise the effects of environmental influences on children's health and wellbeing.

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