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Lead and Cadmium Hair Levels in a Sample of Egyptian Children with Attention Deficit Hyperactivity Disorder

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Abstract

Background: Attention Deficit Hyperactivity Disorder (ADHD) is a common neurobehavioral disorders among children. It has multifactorial mechanisms of induction; one that main mechanism is the exposure to neurotoxins. Environmental exposure to Lead (Pb) and Cadmium (Cd) may be implicated in its development. Objective: This study estimated the correlation between Pb and Cd hair levels and the development of ADHD.

Methods: 102 children were divided into two groups: the ADHD group (n=54) diagnosed with ADHD according to (DSM)-IV, Conner's and intelligence quotient scales, control group apparently healthy children (n=48). Hair samples were taken for estimating Pb and Cd levels using Inductively Coupled Plasma (ICP).

Results: A statistically significant difference was found regarding Pb levels between the study and the control groups with significant increased risks among female patients, inattention type and those with severe Conner's scale, meanwhile, Cd neither showed insignificant differences in hair levels nor increased risks among ADHD subtypes or grades of Conner's scale.

Conclusion: Both metals showed unexpectedly highly elevated levels in study subjects. Lead has a significant relation with weak association to ADHD meanwhile, cadmium had no significant relation.

Keywords: Lead; Cadmium; ADHD; Egyptian

Introduction

Attention-Deficit Hyperactivity Disorder (ADHD) is one of the most common heterogeneous neurobehavioral disorders in children. Worldwide, the prevalence of ADHD is reported to be from 0.2% to 28% [1]. In Egypt, different studies were conducted to estimate prevalence of ADHD. In Menofia governorate, prevalence of ADHD was found to be 6.9% among primary school children [2], which is higher than the results of an earlier study (5.1%) done in the same governorate by Elwan [3] as well as that was conducted in Assuit city which reported 6% prevalence [4]. However, higher prevalence was reported by Suez Canal University Hospital (13.6%) [5]. This disorder is characterized by its pervasive significant functional academic, social and familial impairment to children which may continue throughout adolescence and adulthood. Children with ADHD are at high risk to develop many negative outcomes such as antisocial behavior, conduct disorders and drug abuse [6].

The etiology of ADHD is still controversial with different mechanisms have been implicated to explain it. Previously, genetic predisposition and neurobiological factors constituted its main etiological mechanisms. However, a potential gene-environmental interaction is considered a dominant predisposed theory that poses the role of the neurodevelopmental toxicants and the vulnerability of the developing brain to the environmental pollutants at low levels of exposures that may not affect adults [7], especially in children who are more susceptible to exposure through outdoor play, toys and paint chips [8].

It is estimated approximately that 3% of neurodevelopmental disorders and disabilities are caused by exposure to neurotoxins, inducing neuronal damage; intellectual disabilities, ADHD and autism spectrum disorder [9]. Lead (Pb) and cadmium (Cd) are naturally occurring environmental pollutants that are characterized by being widely proliferating in the environment through human activities, which poses an important public health issue due to their widely approved detrimental health effects, especially for children who are highly susceptible to exposure [10]. In Egypt, River Nile is seriously contaminated with various heavy metals including lead and cadmium [11]. Lead is listed as a well-established neurotoxicant, especially to the child neurodevelopment; its exposure is mainly through diet, air, drinking water and painting [12]. Cadmium is considered a putative neurotoxicant with adverse neurodevelopmental implications. Its exposure could be either occupational, or through cigarette smoking, food and water contamination [13].

Although some reports linked lead toxicity to ADHD [14,15], others failed to correlate cadmium toxicity to ADHD [12]. The aim of this study was to estimate the correlation between lead and cadmium hair levels and the development of ADHD.

Methodology

Subjects

A hospital-based case control study was conducted in Mansoura University Children Hospital from June 2015 to January 2017. All children were matched for age and sex, their ages ranged from 5-14 yrs. Children with severe neurological or psychiatric disorders such as cerebral palsy, mental retardation, seizures, autistic disorders; those with severe birth defects (congenital heart diseases, hereditary metabolic syndrome, and chromosomal anomalies), those on psychotropic medication (e.g. antidepressants), or with chronic organic diseases (deafness, blindness, severe anemia); and those having artificial color treated hair; were excluded from the study.

The study was approved by Institutional Review Board–Mansoura Faculty of Medicine (code no R/16.03.36). Informed consent was obtained from children's parents; as well children above 7 yrs gave assents for participation.

Study design

Children were diagnosed of ADHD according to the medical professional diagnosis, based on Diagnostic and Statistical Manual of mental disorders (DSM)-IV standard according to American Psychiatric Association [16]. As well, initial assessment in the screening stage included the short Ten-Item- Conner's Rating Scale for ADHD [17]. To estimate full scale of Intelligence Quotient (IQ), children completed a 3-subtest short form of the Wechsler [18].

Children were divided into two groups: the ADHD group, 54 children diagnosed with ADHD, they were recruited from Pediatric Neurology Unit. A control group, 48 apparently healthy children were recruited from other Units of the same hospital.

Materials

Lead and cadmium standard solutions, nitric acid (HNO3), hydrogen peroxide (H2O2), distilled water, and acetone, were purchased from Sigma-Aldrich Company, Egypt. All chemicals used were of high purity (certified 99.99%).

Sample collection

Hair samples were taken from all children included in the study. The samples were cut from scalp occipital region using a stainless-steel scissors with hair length varied between 2-5 cm, and weight varied from 0.005^{-1} gm. Hair was collected in dust free polythene bags, thoroughly closed and labeled, digested then sent to Central Toxicology Lab of Tanta University to be analyzed.

Sample digestion

It was conducted in Mansoura Clinical Toxicology Lab of Forensic Medicine and Clinical Toxicology Department according to Perumal and Thangamani [19]; Ishak [20] as follows:

1. Each sample was first washed three times with deionized water, then with acetone, and finally, they were again washed with deionized water. After that they were left to be dried at oven at 110℃ (International atomic energy agency, IAEA).

2. Each dried hair sample was taken in a 50 mL beaker, then to be digested in 10 mL of a mixture of HNO_3 and H_2O_2 (3:1 mL), which was left overnight at room temperature. The content of the beaker was then heated on a plate at 100℃ to obtain a white crystalline residue. It was then re-diluted with deionized water and made up to 35 mL. The blank was prepared the same way but without the hair sample.

Analytical procedure (according to the manufacturer instructions)

1. Serial dilutions were prepared from a stock solution containing 50 mg/L of both Cd and Pb with the following concentrations (1.5, 3, 4.5, 6, 7.5 mg/L) using deionized water.

2. These standards were measured using Inductively Coupled Plasma "ICP" Perkin Elmer Model: Optima 7000 DV Made in Germany, to build up the standard curve.

3. Later, this curve was used to measure the samples by WINLAB32 Software. All samples were adjusted to their weights taken at the beginning of the study. Result of each sample was calculated according to the following equation:

R_s=(35"total amount of dilution for each sample"/weight of the hair sample)×(sample result on ICP). The lower detection limit for Pb was 0.189 mg/L and 0.03 mg/L for Cd.

Statistical analysis

Data was analyzed with SPSS version 21. The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Qualitative data were described using number and percent. Association between categorical variables was tested using chi square. Continuous variables were presented as mean ± Standard Deviation (SD) for parametric data and median for non-parametric data. The two groups were compared with Student t test (parametric data) and Mann-Whitney tests (non-parametric data), while Kruskal-Wallis test was used to compare more than two medians. Spearman correlation was used to correlate non parametric data. Significance of p-value was set at ≤ 5% level.

Results

The study was conducted on 102 children (54 children as a study group, and 48 as control group) recruited from Mansoura University Children Hospital. The mean age of the ADHD group was 8.09 ± 2.22 y, while that of the control group was 7.83 ± 1.94 y with no statistically significant difference between both groups (p=0.535); the highest percentage of patients was among those between 10 to 11 years old and those aged ≤ 6 yrs. In the control group, the highest percentage was among those ≤ 6 yrs as well and those between 8 to 9 years. As regards sex, both groups were sex matched with no statistical significant difference (p=0.792). However, in the study group prevalence of ADHD was higher in female patients than male (63% *vs.* 37%) as shown in Table 1.

Table 2 shows that most of the study group was diagnosed as combined form of ADHD (60.8%); severe degree according to Conner's scale (78.4%), and with mean IQ value of 87.25+11.89.

As shown in Table 3, Pb was detected in 32 patients and Cd was detected in ten patients, out of the ADHD group (n=54). Meanwhile, in control group (n=48), Pb was detected in 35 patients and Cd in seven patients. A statistically significant difference was found regarding Pb levels between the ADHD and the control groups (p=0 . 001). Cutoff values were set for both Cd and Pb equal to median value of the control groups (782.3, 21.78 mg/L for Cd and Pb respectively). A

significant increased risk of exposure five times regarding lead ≥ 21 mg/L was found.

	ADHD group (N=54)	Control group (N=48)	p-value
Sex			
Males	20 (37%)	19 (39.6%)	0.792
Females	34 (63%)	29 (60.4%)	
Age groups (years)			
≤ 6-	13 (24.1%)	14 (29.2%)	0.255
7-	1 (1.9%)	0 (0%)	
8-	8 (14.8%)	14 (29.2%)	
9-	6 (11.1%)	6 (12.5%)	
10-	15 (27.8%)	6 (12.5%)	
11-	2 (3.7%)	0 (0%)	
12-	5 (9.3%)	6 (12.5%)	
13-	4 (7.4%)	2 (4.2%)	
N: number of the subjects; P-value insignificant (<0.05).			

Table 1: Age and sex distribution among the studied groups of children (n=102).

	ADHD group (N=54)	
	n	%
ADHD type		
Hyperactive	11	21.60%
Inattention	9	17.60%
Combined	31	60.80%
Conner's scale		
Mild	2	3.90%
Moderate	9	17.60%
Severe	40	78.40%
IQ (Mean ± SD)	87.25 ± 11.89	
Key: IQ: Intelligence quotient; N: Number; SD: Standard deviation.		

Table 2: Clinical evaluation of attention-deficit hyperactivity disorder of the study group (n=54).

Parameters	ADHD group (N=54)	Control group (N=48)	p-value	OR (95%CI)
Pb (mg/L)				-
n	32	35	Z=3.57	
Median (Min-Max)	73.84 (1.38-173500)	21.78 (1.1-353.9)	p= 0.001*	
Cutoff				5.1 (1.59-16.29)

≥ 21	27 (84.4%)	18 (51.4%)	X2=8.22	
<21	5 (15.6%)	17 (48.6 %)	P=0.004*	
Cd (mg/L)				-
n	10	7	Z=0.781	
Median (Min-Max)	415.6 (0.45-15330)	782.3 (105.5-2035)	p=0.435	
Cutoff				0.32 (0.04-2.41)
≥ 782	3 (30%)	4 (57.1%)	FET	
<782 (r)	7 (70%)	3 (42.9%)	p=0.607	

Cd: Cadmium; Pb: Lead; Z: Mann-Whitney test, OR: Odds ratio; cutoff=Median of control; N: Number; min: Minimum; max: Maximum; mg: Milligram, L: Liter; *: p-value is significant ≤ 0.05.

Table 3: Lead and cadmium hair levels in the studied groups (n=102).

Tables 4 and 5 shows sex and clinical evaluation of ADHD in relation to Pb and Cd levels in the ADHD group at the cutoff values of the median control levels. Regarding Pb, risks were higher among female patients, inattention type and those with severe degree of Conner's scale. For Cd, insignificant increases in risks of exposure were noticed neither among females, ADHD subtypes nor the grades of Conner's scale.

Parameters	**Pb (mg/L)**			**p-value**	**OR (95%CI)**
	Median (Min-Max)	**≥ 21**	**<21**		
		N (%)	**N (%)**		
Sex					
Males	44.1 (1.4-173500)	8 (66.7%)	4 (33.3%)	$\chi 2$= 4.56	r (1)
Females	97.3 (13.8-11040)	19 (95%)	1 (5%)	π (Z) =0.032*	9.5 (1.9-98)
ADHD type					
Hyperactive	66.7 (43-93.5)	4 (100%)	0 (0%)		-
Inattention	2.99 (1.4-911)	4 (57.1%)	3 (42.9%)		13.5 (1.1-65)
Combined	97.5 (20-173500)	18 (94.7%)	1 (5.3%)	P (KW)=0.031*	r (1)
Conner's scale					
Mild	38.1 (4.08-72.1)	1(50%)	1 (50%)		r (1)
Moderate	74.6 (1.4-173500)	3 (60%)	2 (40%)		1.5 (0.05-40)
Severe	95.3 (20.1-11040)	21 (95.5%)	1 (4.5%)	P (KW)=0.042*	21 (0.7-64)

Key: Pb: lead; Z: Mann-Whitney test; KW: Kruskal -Wallis test; OR: odds ratio; CI: confidence interval; N: number; min: minimum; max: maximum; mg: milligram, L: Liter; *: p value is significant ≤ 0.05.

Table 4: Sex and clinical evaluation of ADHD in relation to lead hair levels in the ADHD group positive children (n=32).

Parameters	**Cd (mg/L)**			**p-value**	**OR (95%CI)**
	Median (Min-Max)	**≥ 782**	**<782**		
		N (%)	**N (%)**		
Sex					

Males	141.7 (1.2-15330)	1 (20%)	4 (80%)		r (1)
Females	512.4 (0.45-2508)	2 (40%)	3 (60%)	p (Z)=0.490	2.6 (0.1-45)
Z (p)	0.313 (0.754)				
ADHD type					
Hyperactive	1510 (512-2508)				r (1)
Inattention	318.7 (141-681)	1 (50%)	1 (50%)		-
Combined	7.66 (0.45-15330)	0 (0%)	3 (100%)	P (KW)=0.386	0.7 (0.02-18)
Kw (p)	0.811 (0.667)	2 (40%)	3 (60%)		
Conner's scale					
Mild	411.5 (141-681)	0 (0%)	2 (100%)		-
Moderate	7919 (512-15330)	1 (50%)	1 (50%)		r (1)
Severe	163.2 (0.45-2508)	2 (33.3%)	4 (66.7%)	p (KW)=0.477	0.5 (0.02-12.9)
Kw (p)	1.81 (0.403)				

Key: Cd: cadmium; Z: Mann-Whitney test; KW: Kruskal -Wallis test; OR: odds ratio; CI: confidence interval; N: number; min: minimum; max: maximum; mg: milligram, L: Liter; *: p value is significant ≤ 0.05.

Table 5: Sex and clinical evaluation of ADHD in relation to cadmium hair levels in the ADHD group positive children (n=10).

Parameters	ADHD group				Control group			
	Cd mg/L		Pb mg/L		Cd mg/L		Pb mg/L	
	r	p	r	p	r	p	r	p
Conner's scale	0.1	0.495	-0.13	0.366	-	-	-	-
IQ	-0.265	0.069	0.023	0.876	-	-	-	-

Key: Cd: cadmium; Pb: lead; IQ: intelligence quotient; mg: milligram, L: Liter; P value insignificant (<0.05).

Table 6: Correlations between lead and cadmium hair levels and both Conner's scale and Intelligence Quotient (IQ) findings of children with attention-deficit hyperactivity disorder.

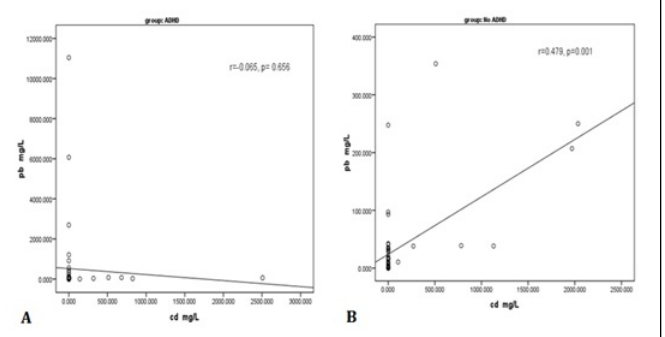

Figure 1: Scatter diagram for correlation between lead (pb) and cadmium (Cd) in (A) ADHD group and (B) control group.

No significant correlations were detected between studied parameters regarding Cd, Pb and clinical evaluation of ADHD in both ADHD and control groups (Table 6), however, a significant weak positive correlation was observed between both Cd and Pb levels in control group (Figure 1).

Discussion

This study was designed to estimate the correlation between lead and cadmium hair levels and the development of ADHD. Authors used scalp hair samples as it represents a permanent record for body metal burden starting from the last six months of exposure [21]. Also, assaying lead and cadmium levels by ICP-MS has high sensitivity and ability to measure a large range of concentrations [20]. Although patients were randomly selected from outpatient clinic, it was found that ADHD female patients were non-significantly predominant than males in a ratio 1.7:1. This is different from many previous studies that reported more predominance in males [1,4,13]. These differences in sex distribution may be due to small sample size of the present study; however, this can be of no clinical significance as most of the etiopathologies for this disease develop in the pre-differentiation period of the children's lives.

Nevertheless, average international reported most prevalent ages ranged from 6-12 yrs [1], most of patients of the present study were in the age groups 10-11 yrs and less than 6 yrs. This may be due to different sample sizes or different study design. However, results of the present study confirms the fact that ADHD is mostly identified in those children first starting school [1,2]. A fact that was confirmed with the results of the present study where 79.7% of the children were in the elementary, while preparatory stage declined only to 20.4%.

The combined form showed the highest prevalent type in the present study followed by the hyperactive then the inattentive. A previous Egyptian study conducted by El-Tallawy [4] in Assuit city

found that the hyperactive type was the most prevalent, then the combined type and lastly the inattentive type. Meanwhile, in United Arab Emeritus UAE, Yousef [8] found that inattentive type was the most prevalent followed by the hyperactive and lastly the combined type. Previously, other study conducted by Wolraich [22], they found that inattentive type (5.4%) was the most frequent type, followed by hyperactive type (4.4%) and finally the combined type (3.6%). As well, Nigg [14] reported that a research conducted on 150 American children, proved that the presence of lead in their blood considerably contributed to a higher incidence of hyperactive and impulsive behavior. However, such a correlation was not found with reference to attention deficit disorder, compared to the control group. Recently, a Spanish study revealed that the prevalence of children with probable ADHD was 5.4% (2.6% inattention subtype symptoms, 1.5% hyperactivity/impulsivity subtype symptoms, and 1.3% combined subtype symptoms) [23]. These differences could be attributed to variability in the degree of awareness to such disorders with the ability to detect cases through family observation to hyperactive child as a source of troubles, as well school early discovery to inattentive type.

The median hair lead level in the in the present ADHD group was 73.84 mg/L with significantly higher difference from those children without ADHD (21.78 mg/L). At levels higher than 21 mg/L, the risk to develop ADHD was 5 times significantly higher than those having levels less than 21 mg/L. Females, inattentive, either moderate or severe Conner's scale were predominantly having significantly higher risk to develop ADHD at levels more than 21 mg/L. Studying the association between lead levels and ADHD using hair samples was scarce. A study was conducted on hair samples of children with ADHD and revealed that children's hair lead concentrations ranged from less than one to 11.3 ppm (μg/g) with an observed significant striking relation between ADHD and hair lead levels [14].

On the other hand, many studies showed that adverse neurodevelopmental effects may occur at 10 μg/dL in blood, and even levels less than 5 μg/dL with 4.1 to 8.7 fold higher risk for cognitive deficits and behavioral problems of ADHD and its related behaviors [6,12,24,25]. A meta-analysis study showed a small to medium association between inattention and hyperactivity symptoms and lead exposure, as well, with decreased IQ and conduct problems [26]. A more recent prospective cohort study was conducted by Ji [27] found that 8.9% of the children had elevated blood lead levels (5-10 μg/dL), which was associated with a 66% increased risk of ADHD; confirming that there is no safe lead threshold in blood to induce such consequences. Different mechanisms have been posed to explain the mechanism by which lead may be implicated to the patho-etiology of ADHD, such as dopamine system dysfunction through alteration of midbrain/striatal dopamine functioning and gene expression in the striatum [6]; or lead induced oxidative stress neural apoptosis, neurotransmitter storage and release, mitochondrial damage, and hippocampal changes [25].

Regarding cadmium levels, the present median value is unexpectedly higher, however insignificant, in the control group (782.3 mg/L) compared to the study ADHD one (415.6 mg/L), with no observed risk to develop ADHD to those at higher values than the median control levels. As well, insignificant risks were countered regarding sex, ADHD subtypes or Conner's scale grades. Similar to the results of this study, other human studies failed to detect significant associations between cadmium exposure and neurodevelopmental consequences such as ADHD [12,28-31]. Meanwhile, Ciesielski [13] stated that there was a possible non-significant decrease in ADHD risk in children who had urinary Cd levels above the first quartile, with OR of 0.50, 0.52, and 0.67 for the second, third, and fourth quartile.

In contrast, a previous experimental study reported by Szkup-Jabłońska [28] proved the potential influence of cadmium on the neurobehavioral functions of the offspring of rats exposed to cadmium oxide, at doses of 0.02-0.16 mg Cd/m^3. This was explained by the influence of cadmium on brain metabolism hindering many sulfhydryl enzymes and consequently, it negatively affects levels of norepinephrine, serotonin and acetylcholine. As well, a meta-analysis study reported that only two human studies evaluated toxic cadmium effects on CNS and found an association with neurodevelopmental or behavioral disorders [29]. These studies proposed that Cd can inhibit calcium flux for neurotransmitter release thereby disrupting the neural communication required for synaptic network formation during neural development, as well, it may influence the proliferation and differentiation of neuroblasts and disrupt thyroid hormone function in vitro [13]. This inconsistency of the results may be accounted to the variability in sample size and design, besides, different exposure metrics and susceptibility.

A weak inverse insignificant association was observed between both lead and cadmium among the study group. However, there was significant weak positive correlation among the control group. Similar findings was stated in the animal study conducted by Kim [12], they showed no difference in behavior between control rats and rats that were given both Pb and Cd in their diets, but they did report differences in the Pb only and Cd only rats suggesting that Cd may have decreased the amount of Pb absorbed into the blood stream. This may be explained by various interactions between the metals within the children bodies as cadmium co-exposure may attenuate lead-mediated increases in activity.

The mean IQ value of the present ADHD group was 87.25. This value is considered to be a low average intelligence value as declared by Bearce [30]. Insignificant weak correlations were observed regarding IQ and Conners' scale with either cadmium or lead levels.

The toxic effect of environmental pollutants on cognitive impairment and reducing IQ scores were confirmed in many studies conducted by Wang [6]; Nigg [24] and Szkup-Jabłońska [28]. They stated that blood lead levels even less than 10 μg/dl were usually associated with reduced intellectual functioning IQ. Regarding cadmium, previous studies reported associations between higher urinary cadmium levels and mental retardation, decreased IQ and behavioral problems especially with concurrently elevated lead levels [13]. They stated that hair cadmium and lead content were significantly correlated with impaired cognitive development especially intelligence scores and school achievement scores, but not motor impairment scores with significant strong effect of cadmium on verbal I.Q., meanwhile, lead has a stronger effect on performance I.Q. Conner's scale is considered to be sensitive and better sensitive tool [24], by correlating the studied toxicant with the scale, we found no significant correlation could be established. These results disagree with Nigg [24], who confirmed that the selected ADHD sample is reliably related to blood lead levels regarding Conner's scale.

Hair cadmium levels were strikingly high even in control group indicating significant sources of exposure. Unfortunately, history regarding exposure to certain types of food and passive smoking which are the most common source of exposure for children were not elucidated. A previous Egyptian study [31] reported mean scalp hairs cadmium levels in healthy children to be 0.02 ± 0.03 (range: 0-0.15)

μg/L and in children with different types of cancers to be 0.43 ± 0.45 (range: 0-3.7) μg/L. These discrepancies highlight the importance to perform screening surveys to estimate the actual levels of exposure among children as a major public health problem.

Conclusion

To the best of our knowledge this is the first study to report on the association between cadmium and lead levels in hair samples of Egyptian children with ADHD. Unexpectedly both metals showed highly elevated levels even in control. Lead has a significant relation with weak association to ADHD meanwhile, cadmium had no significant relation.

Limitation of the Study

Small sample size is considered the main limitation of this study to be able to generalize the unexpectedly high detected lead and cadmium levels using hair samples. It is well established that to clarify the relationship between any environmental toxicants and the risk of developing clinically neurodevelopmental disorders, very large cohort studies with a long follow-up are needed. Another limitation of the study is that the accurate ages of starting exposure and methods (sources) of exposure are not determined in this study to be able to explain the probable causality of the disease to such pollutants.

Recommendations

Children who have ADHD are at increased risk for conduct disorder, antisocial behavior, and drug abuse later in life. In this regard, cohort studies with bigger sample size is recommended to elucidate the actual increase in lead and cadmium levels, and even mixture of metal exposures, and to have proper preventative measures especially to environmental risk factors including heavy metal exposure with sufficient attention is mandatory.

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