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Attention deficit hyperactivity disorder and its association with heavy metals in children from northern Chile

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ABSTRACT

Introduction: Exposure to lead and arsenic has been associated with child behavior problems. In Arica, a northern city of Chile, the natural presence of arsenic in water has been registered. Also, the city has a history of heavy metals contamination of anthropogenic origin. The purpose of this study was to explore the association between the concentration of blood lead and urinary inorganic arsenic with attention deficit hyperactivity disorder (ADHD) as reported by parents.
Methods: Cross-sectional design with data analysis of 2656 children between the ages of 3 and 17 enrolled at the Environmental Health Center of Arica between 2009 and 2015. The diagnosis of ADHD was made based on the parents' response to questions about health history. Multiple logistic regression models were used to adjust for confounding variables.
Results: The prevalence of ADHD was 6.4%. The means urinary inorganic arsenic and blood lead were 21 μg/L and 1.5 μg/dl, respectively. In the lead model adjusted for sex, age, housing material quality and exposure to secondhand tobacco smoke report; children with blood lead concentrations ≥5 μg/dl were more likely to develop ADHD [Odds Ratio (OR): 2.33 95% confidence intervals (CI) 1.32–4.12)]. Regarding arsenic, the adjusted model revealed a higher chance of developing ADHD in the fifth quintile of exposure (OR = 2.02 IC 95% 1.12–3.61).
Conclusion: The findings of this study suggest that exposure of children to lead and inorganic arsenic was associated with ADHD. This study provides additional evidence to existing literature regarding the potential role of toxic metals such as lead and arsenic in children's behavior. However, our findings should be interpreted with caution due to the limitations of the study.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a developmental complication characterized by difficulty in maintaining attention, controlling impulses, and regulating activity levels (American Psychiatric Association, 2013). At least 1 in 10 American children between the ages of 4 and 17 have ADHD (Visser et al., 2014), while a global prevalence was estimated between 5 and 7% (Polanczyk et al., 2007; Thomas et al., 2015). In Chile, 10% of children and adolescents have been diagnosed with ADHD (de la Barra et al., 2013), much of them also have developed complications such as low self-esteem, conflictive relationships, poor academic performance, and increased risk of substance abuse in adolescence, which could have implications in adult life (Harpin, 2005).

Hereditary factors account significantly to the etiology of ADHD (Chang et al., 2013); nonetheless, it has been documented that environmental pollutants may play an essential role in the development of the disease (Goodlad et al., 2013; Marks et al., 2010; Rochester et al., 2018; Rodríguez-Barranco et al., 2013). Numerous studies have reported that exposure to lead is a potential risk factor for ADHD in children (Goodlad et al., 2013; Roy et al., 2009; Wang et al., 2008), even at low concentrations (Braun et al., 2006; Cho et al., 2010; Froehlich et al., 2009; Huang et al., 2016; Kim et al., 2010; Nigg et al., 2010). Contrary to lead, there is little evidence that demonstrates an

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association between arsenic and the development of ADHD (Rodríguez-Barranco et al., 2016; Roy et al., 2011).

It has been reported that soil in the city of Arica has natural arsenic concentrations (Apata et al., 2017). However, the concern for exposure to lead and arsenic began in the late 1980s because of contamination by toxic waste with high concentrations of heavy metals which were imported by a Chilean company to be recycled. The waste was not used and was abandoned in an urban area where years later social housing were built. Additionally, the transport and storage of lead from Bolivia polluted the *Maestranza* and port sector (Tchernitchin et al., 2006). In the late 90s, the toxic waste was removed from the city, and in 2009 the regional government of Arica and Parinacota established an intervention program in exposed areas to control exposure to heavy metals and implemented a comprehensive program against possible health effects of exposure to metals (Gobierno regional de Arica y Parinacota, 2009).

The intervention program included the access of the exposed population to The Environmental Health Center (EHC) of Arica that was put into operation in 2009 with a multi-professional health team. In this framework, a registry of the exposed population was created. The aim of this study was to explore the association between the blood lead and urinary inorganic arsenic concentrations and the ADHD reported by parents in the population under 18 years registered at the EHC between 2009 and 2015.

2. Methods

2.1. Design and study population

In this cross-sectional study, care records from the EHC of Arica between 2009 and 2015 were analyzed. These care records were compiled in the context of Law No. 20,590 which establishes an intervention program in areas with presence of heavy metals in Arica (Ministerio secretaría general de la presidencia, 2012). When children were registered in tha EHC, an informed consent was taken from the parents for lead and arsenic sampling. Socio demographic information was available in the admission form for individuals under 18 years old residing in the contaminated areas known as Sector Puerto, Sector Maestranza and Sector F. These risk zones were identified through a diagnosis of the chemical quality of the Arica's soil (Agriquem, 2009).

2.2. Measures

2.2.1. Blood lead concentration

The *blood lead concentration* was obtained by a venous puncture in the first attention as well. The analysis was performed by atomic absorption spectrophotometry in the Occupational Health Laboratory of the Institute of Public Health (ISP) from 2009 to 2014 and in the Environmental and Occupational Public Health Laboratory in 2015. The limit of detection (LOD) was 0.99 µg/dl. Concentrations below the LOD were assigned a value of half of the LOD (0.495 µg/dl) (Caldwell et al., 2017).

2.2.2. Inorganic arsenic concentration

The *inorganic arsenic concentration* was obtained by a urine sample provided in the first attention. The analysis was carried out in the Occupational Health Laboratory of the Institute of Public Health through atomic absorption spectrophotometry with hydride generation (AAS-HG) from 2009 to 2014 and in the Environmental and Occupational Public Health Laboratory in 2015. The LOD was 1.99 µg/L and concentrations below LOD were assigned a value of 0.99 µg/dl (LOD/2) (Normandin et al., 2014).

2.2.3. Outcome and confounding variables

The outcome variable, *attention deficit hyperactivity disorder (ADHD),* was obtained by the parents' report when the nurse and/or physician performed the anamnesis in the first medical attention. They asked about the children's health history through an open question. Then, health records were available in text format and were transformed into a dichotomous variable, considering the fields where attention deficit and hyperactivity were recorded. Thus, we considered that ADHD was present if the children's health history included the report of both disorders.

Covariables were obtained from the admission form such as socio-demographic variables: sex and age; housing material quality (solid, mixed and light or substandard); anthropometric variables: weight and height to compute body mass index (BMI). The classification of nutritional status was according to the diagnostic criteria of the World Health Organization (WHO). Weight-for-length was the indicator for children under five years of age, and BMI-for-age, for children five and over. Nutritional status was performed with the following classification: underweight ≤ -1 standard deviation (SD), normal > -1 SD and $< +1$ SD, overweight $\geq +1$ SD and $< +2$ SD, and obese $\geq +2$ SD (Ministerio de Salud, 2018). Parent's report of children's exposure to secondhand tobacco smoke and children's playing pattern were also registered into the admission form in the first attention.

2.3. Data analysis

The descriptive analysis was carried out through the estimation of mean and median (measures of central tendency) and standard deviation (SD) and interquartile range (IQR) (measure of dispersion) for continuous variables, while proportions and relative frequencies for categorical variables. To compare blood lead level and inorganic arsenic according to participants characteristics we used non-parametric tests (Mann-Whitney and Kruskal–Wallis), whereas Pearson Chi-square and Fisher's exact test were used to compare the prevalence of attention deficit hyperactivity disorder among covariables.

The association analysis between blood lead, urinary arsenic concentration and ADHD was performed through multiple logistic regression models adjusted for variables described in the literature such as age, sex, exposure to secondhand tobacco smoke (Braun et al., 2006; Roy et al., 2011), and housing material quality as a proxy of socioeconomic status. The results are presented as odds ratios (OR) with their respective 95% confidence intervals (CI).

The joint exposure of lead and arsenic was evaluated to inquire about the potential of a higher effect on the development of ADHD than each metal separately. The interaction term lead*arsenic (both as continuous variables) was created. Moreover, the possible role of exposure to secondhand tobacco smoke as an effect modifier was evaluated. For this end, two interaction terms were generated arsenic*exposure to secondhand tobacco smoke and lead*exposure to secondhand tobacco smoke, considering as modifiers the interaction terms with a P-value < 0.05. Data were analyzed using statistical package STATA v12.0 (StataCorp., College Station, TX, USA).

3. Results

The population under 18 registered in the database encompasses 3190 individuals. There was available medical care information for 2656 individuals, of which 2500 and 2506 had blood lead and urinary inorganic arsenic data, respectively. One observation was considered outlier for having an arsenic value of 312 µg/L and was deleted in the analysis. Complete information was obtained for 78% of the registered subjects.

The average age was 10 (SD 3.8), and 49.6% of the children were male. Regarding body composition, most had normal BMI (48.4%), 20.9% were overweight and 11.5% were obese; however, there was a 37% data loss of this variable. Parents' reported than, 22.3% were exposed to secondhand tobacco smoke (Table 1).

The blood lead mean $\pm$ SD (median, IQR) was 1.5 $\pm$ 1.8 µg/dl (1.0, 0.495–2.0 µg/dl), with a minimum and maximum value of 0.495 and 27 µg/dl. Since the blood lead level did not distribute normally (p-

Table 1
Demographic characteristics of the participants, Arica 2009–2015.

Characteristics	N (%)
Total N = 2656	
Gender	
Female	1267 (50.4)
Male	1245 (49.6)
Age (years)	
3 - 9	1086 (40.9)
10 - 13	820 (30.9)
14 - 17	750 (28.2)
BMI[a] (kg/mt^2)	
Weight deficit	319 (19.2)
Normal	804 (48.4)
Overweight	347 (20.9)
Obesity	192 (11.5)
Housing material quality	
Solid	1324 (50.6)
Mixed	1109 (42.4)
Light (substandard)	184 (7.0)
Parents' report of children exposure to secondhand tobacco smoke	584 (22.3)

[a] BMI = body mass index.

value < 0.001, Shapiro Wilk test), it was dichotomized based on 5 µg/dl, the reference limit set by the Centers for Disease Control and Prevention (CDC) for children (Centers for Disease Control and Prevention, 2017). The proportion of children who presented blood lead levels greater than or equal to 5 µg/dl was 5.5%.

Regarding the concentration of inorganic arsenic in urine, the values did not present a normal distribution (p-value < 0.001, Shapiro Wilk test). The mean ± SD (median, IQR range) was 21 ± 16.9 (18, 9.0–28 µg/L), with a minimum and maximum value of 0.99 and 156 µg/L. Since an exposure threshold has not been established for arsenic in children and considering the distribution of the variable, urinary arsenic levels was categorized into quintiles (Q), with the following cut-off points: Q1, < 7.0 µg/L; Q2, 7.1–14.0 µg/L; Q3, 14.1–21.0 µg/L; Q4, 21.1–31.0 µg/L, Q5, 31.1–156.0 µg/L.

Table 2 describes the concentrations of tested metals children in relation to their sociodemographic characteristics. The concentration of blood lead was slightly higher in male participants, in age younger group, and in those who lived in housing of light (substandard) or mixed material quality. Concerning inorganic arsenic, a slightly higher concentration was observed in the following groups: age group between 14 and 17 years old, overweight and obese, and those living in housing of light material quality.

Out of the tested children, 8.1, 10.4 and 6.4% were hyperactive, attention deficit, and with both attention deficit hyperactivity disorder, respectively. A higher proportion of ADHD was observed in male sex (10.2%), in the age group between 10 and 13 years old (9.8%), in those who live in housing of light material quality (9.2%) and in child whose parents reported they have been exposed to secondhand tobacco smoke (8.9%) (Table 3).

Table 3
Prevalence of attention deficit hyperactivity disorder according to the characteristics of the participants, Arica 2009–2015.

Characteristics	N (%)	P value[a]
Gender		< 0.001
Female	36 (2.7)	
Male	134 (10.2)	
Age (years)		< 0.001
3 - 9	54 (4.9)	
10 - 13	80 (9.8)	
14 - 17	36 (4.8)	
BMI (kg/mt^2)		0.182
Weight deficit	30 (9.4)	
Normal	49 (6.1)	
Overweight	30 (8.7)	
Obesity	15 (7.8)	
Housing material quality		0.267
Solid	82 (6.2)	
Mixed	69 (6.2)	
Light	17 (9.2)	
Parents' report of children exposure to secondhand tobacco smoke		0.005
No	115 (5.6)	
Yes	52 (8.9)	

[a] Pearson Chi-square test and Fisher's exact test for categorical variables. BMI = body mass index.

Table 2
Description of the level of blood lead and urinary inorganic arsenic according to characteristics of the participants, Arica 2009–2015.

Characteristics	Lead (µg/dl)		Arsenic (µg/L)	
	Median (IQR range)	P value[a]	Median (IQR range)	P value[a]
Gender		0.022		0.119
Female	0.495 (0.495–2.0)		17.0 (9.0–28.0)	
Male	1.0 (0.495–2.0)		18.0 (10.0–28.3)	
Age (years)		< 0.001		< 0.001
3 - 9	1.0 (0.495–3.0)		13.0 (6.0–24.0)	
10 - 13	0.495 (0.495–2.0)		19.0 (11.0–30.0)	
14 - 17	0.495 (0.495–1.0)		20.0 (13.0–30.0)	
BMI (kg/mt^2)		0.049		0.005
Weight deficit	1.0 (0.495–2.0)		17.5 (10.0–29.0)	
Normal	0.495 (0.495–2.0)		19.0 (11.0–30.0)	
Overweight	0.495 (0.495–2.0)		21.0 (14.0–34.5)	
Obesity	0.495 (0.495–2.0)		21.0 (13.0–30.0)	
Plays on the floor		< 0.001		0.475
No	0.495 (0.495–2.0)		18.0 (9.0–28.0)	
Yes	1.0 (0.495–2.0)		17.0 (9.0–28.0)	
Housing material quality		< 0.001		0.038
Solid	0.495 (0.495–2.0)		17.0 (9.0–28.0)	
Mixed	1.0 (0.495–2.0)		18.0 (10.0–28.0)	
Light or substandard	1.0 (0.495–2.0)		20.0 (10.0–34.0)	
Parents' report of children exposure to secondhand tobacco smoke		0.095		0.794
No	0.495 (0.495–2.0)		18.0 (9.0–28.0)	
Yes	1.0 (0.495–2.0)		17.0 (9.0–27.5)	

[a] Wilcoxon rank-sum test (Mann-Whitney) for dichotomous variables and Kruskal Wallis test for categorical variables. BMI = body mass index.

Table 4
Association between exposure to heavy metals and ADHD as reported by parents, Arica 2009–2015.

Variables	OR (CI 95%)	P-value	OR (CI 95%)[a]	P-value
Lead ≥5 μg/dl	2.14 (1.25–3.65)	0.005	2.33 (1.32–4.12)	0.004
Quintiles As-i μg/L				
Q1 (≤7.0)	1.00		1.00	
Q2 (7.1–14.0)	1.92 (1.09–3.38)	0.024	1.72 (0.96–3.08)	0.066
Q3 (14.1–21.0)	2.09 (1.19–3.67)	0.010	1.74 (0.96–3.13)	0.066
Q4 (21.1–31.0)	1.87 (1.04–3.35)	0.035	1.72 (0.94–3.15)	0.080
Q5 (31.1–156.0)	2.23 (1.27–3.91)	0.005	2.02 (1.12–3.61)	0.019

[a] Adjusted by age (years), sex (0: female and 1: male), parents' report of children exposure to secondhand tobacco smoke (0: not exposed and 1: exposed) and housing material quality (1: solid, 2: mixed and 3: light or substandard). As-i = Inorganic arsenic concentration. OR= Odds Ratio. CI= Confidence intervals.

3.1. Association analysis

Children with lead concentrations ≥5 μg/dl have a 2.33 times higher chance of developing ADHD (95% CI 1.32–4.12) when the logistic regression model was adjusted for age, sex, exposure to secondhand tobacco smoke, and housing material quality (Table 4). Regarding the association between ADHD and inorganic arsenic in quintiles, the adjusted model showed a higher association in the fifth quintile (OR = 2.02 95% CI 1.12–3.61) (Table 4).

Regarding the assessment of a potential modifier effect, no interaction was found between both metals nor with exposure to secondhand tobacco smoke reported by parents (data not shown).

4. Discussion

The results of this exploratory analysis reveal that concentrations of blood lead and urinary inorganic arsenic could be associated with ADHD as reported by parents. Children who had a blood lead level ≥5 μg/dl have a two times higher risk of developing ADHD whereas, in inorganic arsenic, a greater risk is observed only when urinary inorganic arsenic concentration is in the highest quintile.

Based on parents' report, the prevalence of ADHD of children under this study was 6.4%, which is similar to the ones reported in two meta-analyses of 5.3% (Polanczyk et al., 2007) and 7,2% (Thomas et al., 2015). In Chile, De la Barra et al. determined a prevalence of 10% in children (de la Barra et al., 2013). This difference could be attributed to the method of measuring ADHD. De la Barra et al. obtained the diagnosis with the Diagnostic Interview Schedule for Children instrument (DISC-IV). In this study, the ADHD diagnosis was obtained through the report of the parents or guardians, which could contribute to an underestimation of the prevalence because lack of proper diagnosis.

The association between lead exposure and symptoms of ADHD has been previously reported (Goodlad et al., 2013). In this study, 5% of the children had blood lead concentrations equal to or greater than 5 μg/dl; in which they were 2.33 times more likely to have ADHD, as reported by the parents (95% CI: 1.32–4.12). This result is consistent with studies that have found an association in children with higher blood lead exposure (≥2.0 to ≥10 μg/dl) (Braun et al., 2006; Liu et al., 2014; Roy et al., 2009; Wang et al., 2008).

The evidence of the association between arsenic and ADHD is limited (Rodríguez-Barranco et al., 2016, 2013; Roy et al., 2011). In the current study, a greater association was only observed in the fifth quintile of exposure (OR = 2.02 95% CI: 1.12–3.61). In a cross-sectional study, a dose-response relationship between total urinary arsenic tertiles and a lack of attention and impulsivity was described (Rodríguez-Barranco et al., 2016). In another cross-sectional study, though a dose-response relationship between the ADHD index and quartiles of urinary inorganic arsenic was not observed, the third quartile evidenced a significant association (OR = 2.4 (1.1–4.9) (Roy et al., 2011). In a study that evaluated arsenic and cognitive development a greater association was seen in lower category of urinary arsenic, which was attributed to the lack of statistical power and variability in the group with the greatest exposure (Rosado et al., 2007).

Research at the national level showed two studies related to the emission of pollutants from the Ventanas industrial complex. The first study revealed that children from La Greda school had average urinary arsenic and blood lead concentrations of 12.5 μg/L and 2.6 μg/dl respectively. Besides, the Behavior Rating Inventory of Executive Function (BRIEF) test revealed that students of the La Greda school had a 1.53 times higher chance of developing attention deficit syndrome or a learning disorder, compared to children from a non-exposed school; however, the association was not statistically significant (Departamento de Salud Pública Pontificia Universidad Católica de Chile, 2011). The second study, nested in the first one, analyzed the frequency of ADHD in 99 children of La Greda school found a prevalence of ADHD of 23%. Differences in the concentrations of urinary arsenic, blood lead and ADHD diagnoses between both groups were evaluated and no statistically significant differences were reported (Luksic, 2016) due to small sample size.

It should be noted that ADHD is characterized by the difficulty the individual has to maintain attention, motor restlessness, and impulse control. Its expression is multicausal, where the genetic component is relevant to the risk; nonetheless, psychosocial, ethnic, educational, and environmental aspects play a fundamental role (Carrasco et al., 2012; Lagos et al., 2011; Puddu et al., 2017). The origin of the pathology was related to different reasons such as the dysfunction of the dopamine system, neurotransmitter linked to different processes of the central nervous system, including attention and motor activity (Carrasco et al., 2004; DiMaio et al., 2003). The mechanism of action underlying the identified association in this study might be related to the effect of lead on the neurotransmission of dopamine (Jones and Miller, 2008; Szczerbak et al., 2007), or to the epigenetic changes linked to ADHD induced by exposure to this same metal (Luo et al., 2014). The evidence on the role of arsenic in the alteration of the dopamine system is inconsistent (Rodríguez et al., 2003). Although it has been shown that early exposure to arsenic produces dopaminergic alterations increasing the sensitivity of receptors that are related to hyperactivity (Chandravanshi et al., 2014). Furthermore, the neurotoxic effect of arsenic has been attributed to its ability to induce oxidative stress in the brain (Rodríguez et al., 2003), which also seems to be related to the disruption of the dopamine system (Chandravanshi et al., 2014). However, more research is needed to generate an explanatory neurobiological hypothesis associated with exposure to heavy metals and ADHD.

This study has inherent limitations of data from a surveillance system. First, a cross-sectional study does not ensure that the exposure preceded the effect. Second, ADHD data were through the parents' report, so it cannot be ruled out information bias. Nevertheless, the prevalence of ADHD estimated in this study is similar to that estimated worldwide (Polanczyk et al., 2007; Thomas et al., 2015). Third, urinary creatinine was not measured to adjust for urinary flow variations. Fourth limitation was missing data: *educational level of the parents* (59%), *ethnicity* (73%), and potential confounders that were not measured as a diagnosis of ADHD of the parents and family socioeconomic status.

5. Conclusion

In this population, exposure to lead and arsenic was independently associated with ADHD. These results are consistent with previous published work that has already revealed that both metals are potential neurotoxic for development. However, our findings should be interpreted with caution due to the limitations of the study. Measures to reduce exposure in children should be of concern since behavioral disorders have implications for the well-being of children with profound consequences in adult life. Based on the results, it is suggested to continue monitoring the exposure to lead and arsenic, improve the completeness of the registry, and perform the diagnostic measurement of ADHD through a validated instrument.

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Declaration of competing interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

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