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Cognitive performance among cohorts of children exposed to a waste disposal site containing heavy metals in Chile

Soledad Burgos, Marcela Tenorio, Pamela Zapata, Dante D. Cáceres, José Klarian, Nancy Álvarez, Renato Oviedo, Rosario Toro-Campos, Luz Claudio, and Verónica Iglesias

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ABSTRACT

Between 1984 and 1998, people living in Arica were involuntarily exposed to metal-containing waste stored in the urban area. The study aims to determine whether children who lived near the waste disposal site during early childhood experienced negative effects on their cognitive development. The cognitive performance was assessed using the Wechsler Intelligence Scale for Children. The exposure variable was defined by the year of birth in three categories: (1) Pre-remediation (born before 1999); (2) During-remediation (born between 1999 and 2003); and (3) Post-remediation (born after 2003). In the crude analysis, a difference of 10 points in the IQ average was observed between the group born in the pre- (81.9 points) and post-remediation period (91.1 points). The difference between both groups was five times higher as compared to children of similar age and socioeconomic status in other cities of Chile. This result could be related with a period of high potential for exposure to this contaminated site.

Introduction

Contaminated sites are a great concern for nearby populations due to the health effects of pollution (Kah et al. 2012). In addition, people who live near these contaminated sites are generally low-income families with a higher level of vulnerability to the toxic effects of pollutants. Some evidence from geo-statistical studies reflects that the distribution of learning disorders and other health outcomes coincides with the historical presence of significant sources of heavy metals and contextual factors such as low quality of housing, poverty, low educational attainment of the parents, and other factors associated with the neighborhood (Margai and Henry 2003; Rauh et al. 2008; Olivas-Calderon et al. 2015; Tsuji et al. 2015; Govarts et al. 2016; Zeng et al. 2016). This issue of environmental injustice has been documented throughout the world in many different countries (Cutter 2006; Claudio 2007).

Between 1984 and 1989, the PROMEL Ltd. Company (Metal Processing Company) brought 20,901 tons of toxic waste classified as ‘sludge with metal content’ from Sweden, to the city of Arica (Northern...
Chile) to be recycled. The waste was collected and abandoned in an urban area of the city. Between 1991 and 1996, social housing was built in sectors neighboring the waste disposal site (the neighborhoods known as ‘Los Industriales’, ‘Cerro Chuño’, ‘Sector F’ and other nearby areas). Approximately 15,000 people were exposed, and the majority was low-income families. An analysis of the composition of the sludge showed high concentrations of heavy metals, including arsenic, cadmium, copper, and lead (Figueroa 1997; Tchernitchin et al. 2006). Lead exposure received more attention because it had been proven to have negative effects on child development (Lanphear et al. 2005; Miranda et al. 2007; Bellinger 2008; Jusko et al. 2008; Nigg et al. 2008; Skerfving et al. 2015). In 1998, the local authority of Ministry of Health measured blood lead levels (BLLs) to 3240 children under 14 years of age. The results showed that 3.7% of them had BLLs above 10 μg/dL (Tchernitchin et al. 2006).

After these studies were conducted, the waste disposal site was removed from the urban area in late 1998. The local authority of Ministry of Health took actions to reduce the dispersion of residual dust, by cleaning the roofs of the houses and decontaminating other locations in the city (Tchernitchin et al. 2006). In 2009, a program was implemented to monitor the lead and arsenic concentrations in the bodies of the children living in contaminated areas. Children were treated at the Center of Environmental Health, depending of the Ministry of Public Health. In 2011, 180 of these children participated in a cross-sectional study that sought to assess the relationship between the current lead and arsenic concentrations and their total intellectual quotient and no association was found (Iglesias et al. 2012). However, the effect of being born in different remediation periods was not assessed.

The underlying hypothesis is that the population was affected by an environmental intervention process that lasted for almost a decade and that could have resulted in decreasing exposure levels due to the remediation of the concerned site. Researchers assume that if the waste disposal was removed in 1998 and the abatement measures were effective over time, children born after that key date must have had lower exposure compared to children who were born and lived in this area before 1999. To assess this, the present study aims to determine whether or not children who lived near the waste disposal site during early childhood experienced negative effects on their cognitive development as measured by comparing the intellectual quotient score between three cohorts born in different remediation periods.

**Materials and methods**

**Area of study**

Arica is located on the extreme north of Chile. Its climate is a desert–coastal climate, with temperatures averaging 18 °C and with minimal variations during the year. It has an area of 8726.4 km² and a population of 2,10,920 inhabitants, of which approximately 25.7% are under the age of 15 (Instituto Nacional de Estadísticas). The poverty rate is below the national average (8.2 vs. 11.4%). However, there is a higher level of precarious housing (22.6 vs. 13.1%) (Ministerio de Desarrollo Social 2012). The average level of education is 10.9 years, which is similar to the national average (Encuesta CASEN 2011).

**Study design, population and sample selection**

Between November 2011 and March 2012, a cross-sectional study was conducted using a sample of children from the city of Arica. These children resided in neighborhoods classified as being ‘areas of high environmental risk’ (‘Los Industriales’, ‘Cerro Chuño’, and ‘Sector F’) because of their proximity to waste disposal sites that contained heavy metals, such as lead and arsenic, and were treated at the Center of Environmental Health. The sampling frame consisted of 735 children from 6 to 15 years old. The sample of the primary study corresponded to 180 children, who were selected randomly. Families were visited in their homes and were invited to participate. Each parent/caregiver was requested to sign an informed consent before conducting both the interview and the psychometric test.
Variables

Cognitive performance was measured using the Wechsler Intelligence Scale for Children, Third Edition-Chilean version (WISC-IIIv.ch), which has been previously validated in Chile (Ramírez & Rosas 2007). The variables studied are as follows: Total Intelligence Quotient (total IQ), Execution Intelligence Quotient (execution IQ), and Verbal Intelligence Quotient (verbal IQ). The four factorial indexes included in the test are defined as follows: Verbal Compensation Index, Perceptual Organization Index (POI), Processing Speed Index, and Absence of Distractibility Index (ADI). For all these variables, the results were expressed as a score derived from the coefficient of the deviation of a normal curve with an average of 100 and a standard deviation of 15.

The exposure variable was the birth cohort grouped in three categories according to the period of remediation of the waste disposal site: The first cohort of children born prior to the removal of the waste disposal facility (births prior to 1999) was classified as Pre-Remediation, coinciding with the period of higher exposure. The toxic waste was brought to the area during this period (1984–1989) and accumulated until 1998, after a state of ‘Environmental Emergency’ was declared in the area. Children born between 1999 and 2003 correspond to the intermediate exposure group called cohort born During-Remediation, because the primary environmental intervention was the relocation of the waste disposal in 1999. Finally, children born after 2003 were grouped in the third cohort called Post-Remediation (Figure 1). Researchers assumed that this group had the lowest exposure because the remediation actions were progressive and extended through the date of this research.

Maternal intellectual quotient was measured using the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) (Rosas et al. 2014).

The age, sex, number of siblings, birth order among siblings, number of household members, education level of the parents, family income, address, type of school attended (public, subsidized, or private), and health history of the children or participants were determined using a questionnaire. Other exposure variables such as the presence of smokers at home, the use of waste material on the household construction, time living in the same household since birth, and location of the house were registered in order to describe the residential characteristics of the children’s family. In addition, the local authority of the Ministry of Health provided BLLs and urine arsenic level of children collected between 2009 and 2010 when the children visited the Center of Environmental Health for the first time.

Data collection

Psychometric tests (WISC-IIIv.ch and WAIS-IV) were performed in the facilities of the psychosocial intervention research center of the University of Tarapaca (CEINPSI). Five evaluators trained by researchers from the Center for the Development of Inclusion Technologies (CEDETI) of the Catholic University of Chile applied the tests. The tests were conducted following a protocol in which the adult guardian was contacted, the criteria for participation in the study were corroborated, and the informed consent was obtained. Positive reinforcement was used to engage the participation of the mothers.
and children in the study. The assessment was conducted in children and mothers at the same time in different rooms. Each evaluation lasted between 60 and 90 min.

The sociodemographic and environmental exposure data were collected using a questionnaire that included questions previously used for the characterization of populations from the north of the country and were previously standardized for use in this region (Iglesias et al. 2008). The study was approved by the Ethics Committee of the Faculty of Medicine, University of Chile.

**Statistical analysis**

All the analyses were performed using the statistics program STATA 12.0 (StataCorp LP, Texas, US). Exploratory and descriptive data analyses were performed and new variables were generated. Proportions were used to describe dichotomous and categorical variables, and measures of central tendency and dispersion for continuous variables. Sociodemographic, family characteristics, and environmental exposure measured on a categorical scale were compared between the three cohorts using a $\chi^2$ test and a significance level of 0.05. The age of the children, maternal intellectual quotient, academic educational level of the parents, BLLs, and urine arsenic concentration were compared using the Kruskal–Wallis test. The cognitive performances of the children were compared between the cohorts using an analysis of variance (ANOVA), assuming that the variances were different. In order to explore differences between the cognitive performance of cohorts born in Arica, we run a linear regression model adjusted by confounders.

**Results**

The birth cohorts varied in terms of the age and education of the parents (Table 1). No differences were observed between the cohorts in the total IQ of the mothers, birth position between siblings or other socio-economic characteristics such as income and home ownership. The reports on the sources of soil contaminants, the neighborhood, time of residency in the current home, and passive exposure to tobacco smoke were similar among the three birth cohorts. Regarding to the BLLs, the median was 2 $\mu$g/dl in the three birth cohorts without showing a statistical difference ($p = 0.059$). In the case of urine arsenic concentration, no significant difference among the three cohorts was observed ($p = 0.369$) (Table 1).

The crude analysis shows that cognitive performances were higher in the Post-Remediation births cohort. In this group, the total IQ, verbal and execution IQ, verbal compensation indexes, and POI were significantly different from the other groups (Table 2). Furthermore, the total IQ was 10 points lower in the Pre-Remediation cohort (children born prior to 1999), in comparison with the Post-Remediation cohort (children born after 2003). A similar trend was identified for the component of execution and the perpetual organization index when the Pre-Remediation cohort was compared with the Post-Remediation cohort. The Processing Speed Index and the ADI were the only components that did not show significant differences between cohorts ($p > 0.05$). After adjusting for age, sex, maternal IQ and paternal education, the average difference in total IQ between cohorts increases (Pre-remediation cohort as reference; During remediation $\beta = 9.97$; 95% CI 0.82 to 19.13; Post remediation $\beta = 16.14$; 95% CI 1.53 to 30.74).

**Discussion**

The total IQ, verbal and execution IQ, verbal comprehension index and the POI were significantly higher in the Post-Remediation birth cohort. Children born in Pre-Remediation had an average total IQ of 81.9 points, while children born in Post-remediation period had an average total IQ of 91.1 points. This difference was compared with results obtained in a nationwide study to validate WISC-IIIv.ch (Ramírez & Rosas 2007). In that study, the difference in total IQ, considering the same age groups than children in our study was 0.06 points (Table 3). A second comparison took into account in children
from a city with similar geographic characteristics than Arica (Coquimbo) and considered only subjects of low socioeconomic status (similar to the subjects who participated in the current study). The results in Coquimbo, considering the same age groups than children in our study, showed a difference of 2 points in total IQ, a difference that is five times lower than the value observed in children from Arica (Table 3). Moreover, when comparing children between 12 and 16 years from Arica (mainly children of low socioeconomic status) with the total IQ observed nationwide (including all socioeconomic levels) the difference is close to 20 points (Table 3).

There are several possible explanations for these findings. The birth cohorts represent different periods of exposure during the contamination and remediation process in the city. Particularly, the older cohort exhibited a reduced cognitive performance (12 to 16 year-old children). They were born during the Pre-remediation period, which is in agreement with a period of higher exposure. This greatest

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Table 1. Description of the socio-demographic and exposure variables of participants according to birth cohort, Arica, 2011–2012.

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Socio-demographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Sex, %</td>
<td>40.68</td>
<td>47.27</td>
<td>39.39</td>
<td>0.654</td>
</tr>
<tr>
<td>Age (years), Average (SD)</td>
<td>13.52 (1.27)</td>
<td>10.03 (0.84)</td>
<td>7.12 (0.81)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Maternal intellectual quotient, Average (SD)</td>
<td>84.25 (16.64)</td>
<td>87.51 (13.97)</td>
<td>85.18 (14.43)</td>
<td>0.563</td>
</tr>
<tr>
<td><strong>Education (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father, Average (SD)</td>
<td>10.03 (3.16)</td>
<td>11.05 (2.67)</td>
<td>11.37 (2.08)</td>
<td>0.027</td>
</tr>
<tr>
<td>Mother, Average (SD)</td>
<td>10.32 (3.47)</td>
<td>10.96 (2.86)</td>
<td>11.30 (2.47)</td>
<td>0.339</td>
</tr>
<tr>
<td>Birth order among siblings, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>32.20</td>
<td>29.09</td>
<td>31.82</td>
<td>0.642</td>
</tr>
<tr>
<td>Second</td>
<td>15.25</td>
<td>34.55</td>
<td>30.30</td>
<td></td>
</tr>
<tr>
<td>Third</td>
<td>28.81</td>
<td>10.91</td>
<td>19.70</td>
<td></td>
</tr>
<tr>
<td>Fourth or more</td>
<td>23.73</td>
<td>25.45</td>
<td>18.18</td>
<td></td>
</tr>
<tr>
<td><strong>Household income by month, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;109 USD</td>
<td>10.17</td>
<td>7.27</td>
<td>12.31</td>
<td>0.889</td>
</tr>
<tr>
<td>Between 109 and 340 USD</td>
<td>62.71</td>
<td>65.45</td>
<td>53.85</td>
<td></td>
</tr>
<tr>
<td>Between 341 and 849 USD</td>
<td>18.64</td>
<td>25.45</td>
<td>26.15</td>
<td></td>
</tr>
<tr>
<td>&gt;849 USD</td>
<td>8.47</td>
<td>1.82</td>
<td>7.69</td>
<td></td>
</tr>
<tr>
<td><strong>Housing, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Owned</td>
<td>76.27</td>
<td>65.45</td>
<td>59.38</td>
<td>0.118</td>
</tr>
<tr>
<td>Rented</td>
<td>11.86</td>
<td>9.09</td>
<td>7.81</td>
<td></td>
</tr>
<tr>
<td>Relinquished</td>
<td>0.00</td>
<td>1.82</td>
<td>4.69</td>
<td></td>
</tr>
<tr>
<td>Living with relatives</td>
<td>11.86</td>
<td>23.64</td>
<td>28.13</td>
<td></td>
</tr>
<tr>
<td><strong>Exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household construction using waste material, %</td>
<td>22.03</td>
<td>16.36</td>
<td>24.62</td>
<td>0.536</td>
</tr>
<tr>
<td>Living in the same household since birth, %</td>
<td>66.07</td>
<td>61.82</td>
<td>69.23</td>
<td>0.694</td>
</tr>
<tr>
<td>Presence of smokers in house, %</td>
<td>25.42</td>
<td>25.45</td>
<td>26.15</td>
<td>0.994</td>
</tr>
<tr>
<td>Area where the house is located, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Los Industriales</td>
<td>30.51</td>
<td>30.91</td>
<td>21.21</td>
<td>0.565</td>
</tr>
<tr>
<td>Sector F</td>
<td>64.41</td>
<td>69.09</td>
<td>75.76</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5.08</td>
<td>0.00</td>
<td>3.04</td>
<td></td>
</tr>
<tr>
<td>Blood lead (μg/dL), Median (P25–P75)</td>
<td>2 (1–2)</td>
<td>2 (1–2)</td>
<td>2 (1–4)</td>
<td>0.059</td>
</tr>
<tr>
<td>Urine inorganic arsenic (μg/L), Median (P25–P75)</td>
<td>20 (13–30)</td>
<td>17.5 (11–26)</td>
<td>20 (11–31)</td>
<td>0.369</td>
</tr>
</tbody>
</table>

[^a]: χ² test or Kruskal–Wallis test.
[^b]: Measured between 2009 and 2010.
Table 2. Comparison of the intellectual quotients according to the birth cohorts, Arica, 2011–2012.

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Total intelligence quotient, Average (SD)</td>
<td>81.95 (15.22)(^B)</td>
<td>88.73 (10.61)</td>
<td>91.11 (15.49)(^B)</td>
<td>0.001</td>
</tr>
<tr>
<td>Verbal intelligence quotient, Average (SD)</td>
<td>79.54 (14.95)(^B)</td>
<td>86.62 (13.09)(^B)</td>
<td>88.59 (14.57)(^B)</td>
<td>0.001</td>
</tr>
<tr>
<td>Execution intelligent quotient, Average (SD)</td>
<td>88.63 (15.13)(^B)</td>
<td>93.51 (9.92)</td>
<td>95.95 (16.29)(^B)</td>
<td>0.016</td>
</tr>
<tr>
<td>Verbal compensation index, Average (SD)</td>
<td>79.54 (14.95)(^B)</td>
<td>86.62 (13.09)(^B)</td>
<td>88.59 (14.57)(^B)</td>
<td>0.001</td>
</tr>
<tr>
<td>Perceptual organization index, Average (SD)</td>
<td>88.61 (15.22)(^B)</td>
<td>94.36 (10.19)</td>
<td>96.14 (16.24)(^B)</td>
<td>0.011</td>
</tr>
<tr>
<td>Processing speed index, Average (SD)</td>
<td>91.56 (16.08)</td>
<td>93.69 (13.82)</td>
<td>96.68 (17.30)</td>
<td>0.196</td>
</tr>
<tr>
<td>Absence of distractibility index, Average (SD)</td>
<td>88.25 (16.40)</td>
<td>93.31 (13.38)</td>
<td>89.47 (16.97)</td>
<td>0.207</td>
</tr>
</tbody>
</table>

\(^A\)ANOVA.
\(^B\)Differences between cohorts.

Table 3. Comparison of the total intellectual quotient between children of the same age groups studied in Arica with those participating in the nationwide study to validate WISC-IIIv.ch.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total IQ in children</th>
<th>Difference of averages (total IQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n 6–8 years</td>
<td>n 12–16 years</td>
</tr>
<tr>
<td>Nationwide total IQ punctuation(^A)</td>
<td>524(^B)</td>
<td>99.72</td>
</tr>
<tr>
<td>Coquimbo total IQ punctuation(^B)</td>
<td>31(^B)</td>
<td>94.82</td>
</tr>
<tr>
<td>Arica total IQ punctuation(^C)</td>
<td>66(^C)</td>
<td>91.11</td>
</tr>
</tbody>
</table>

Notes: IQ: Intellectual quotient.
\(^A\)Nationwide study to validate WISC-IIIv.ch. Data from the regions of Coquimbo, Valparaíso, Metropolitan and Araucanía considering all socioeconomic status. Adapted from data provided by the authors of the study.
\(^B\)Nationwide study to validate WISC-IIIv.ch. Coquimbo data considering only low socioeconomic status. Adapted from data provided by the authors of the study.
\(^C\)Data from our study in Arica, mainly low socioeconomic status.

exposure is corroborated by local reports and studies that reported the presence of heavy metals in soil samples (Figueroa 1997; Comisión Especial Investigadora Honorable Cámara de Diputados 2003). This environmental context was present during the early stages of childhood which is consistent with the natural period of human vulnerability related to the immaturity of the nervous system and the high absorption rate of toxicants while young (Sanders et al. 2015, Zeng et al. 2016).

Antecedents of the actions taken by the local authority of Ministry of Health indicate that measures to mitigate the contamination have been implemented since 1999. The waste heavy metals-containing disposal site was removed (Comisión Especial Investigadora Honorable Cámara de Diputados 2003), and a set of complementary remediation actions were carried out. The study conducted in 2011 showed low BLLs (median 2 μg/dL) in the three cohorts with the 96.1% of the values under 5 μg/dL and 100% under 10 μg/dL. This last piece of data coincides with a period of advanced remediation, which is in agreement with the lower-exposure period of current cohorts.

Alternatives explanations for the lower total IQ in older children are related to the Flynn effect. The Flynn effect has been described as the improvement of the total IQ of succeeding generations (Espinosa et al. 2006). As mentioned above, the current study compared its results with the results of a study conducted nationwide for the purpose of validating WISC-IIIv.ch (Ramírez & Rosas 2007). The results do not support the notion that total IQ scores can be attributed to the Flynn effect or age
differences Table 3. Socioeconomic status and maternal total IQ, which have been described as important factors that affect child stimulation and child total IQ (Tong & Lu 2001; Koller et al. 2004) neither show differences between the cohorts. Therefore, it is unlikely that these variables are responsible for the observed variations in total IQ in the current study.

In Chile, there are few studies of the long-term consequences of living near toxic’s disposal sites or assessments of changes in exposure related to management and remediation actions. Research has focused on measuring levels of exposure among the population (Sepulveda et al. 2000; Lisboa et al. 2016). An investigation conducted in the city of Antofagasta in the North of Chile sought to assess whether past (1998) and current (2005) BLLs from an old mineral disposal site with high lead content (removed from the city in 1998) were associated with total IQ. The study showed that current BLL was associated with a significant decrease in total IQ ($p$-value = 0.03), also that BLLs decreased from 8.7 μg/dL in 1998 until 3.2 μg/dL in 2005 in the same children (Iglesias et al. 2011). However, that study did not have available a cohort born after the removal of mineral disposal site, so it was not possible to compare cohorts born in different exposure periods as in the present research.

An additional antecedent in Arica is that the problem generated by the waste disposal site was initially invisible, and subsequently generated a political-environmental conflict involving various stakeholders: community, businesses and public health authorities. As a result, there was little access to health data. This limitation, along with the absence of individual exposure data measured prior to the remediation period, motivated this cohort analysis. The proxy of exposure used in this analysis (birth cohort) was the best option of resolving this uncertainty. Another limitation in this study is the lack of data to quantify the environmental stimulation which could have a direct relationship with higher intellectual performance. The application of the Home Observation for Measurement of the Environment (HOME) inventory would have remedied this lack of information, however since it is required that a psychologist apply the scale in the house, it was not possible to implement this measurement. We don't know if this lack of information could bias the result.

One strength of this research is that it is the first study in Chile that uses a combination of WISC-IIIv.ch and WAIS-IV (standardized version for Chile) to evaluate the cognitive performance of both children and their mothers. This type of evaluation had been conducted only once before. This occurred in a previous study in Antofagasta (Iglesias et al. 2011), which used WISC-r (Calderón et al. 1980) and WAIS (Hermosilla 1982) before these new versions had been validated in the country. Another strength of this study is that researchers had access to part of the original data of the validation study of the Chilean population. This allowed them to compare the total IQ scores of different birth cohorts in relation to a reference value.

**Conclusions**

The lower levels of cognitive performance found among children 12–16 years of age coincides with have been born in the period of greatest exposure to the toxic waste disposal, the Pre-Remediation period. The results suggest that the removal of the disposal site for toxic waste resulted in reduced current levels of heavy metals – as BLLs – which coincides with the higher total IQ score found in the most recent birth cohorts. This is important for health and education policy because the low total IQ score among members of the older cohort might have consequences for school performance and therefore, require a greater educational and psychosocial support. International studies show that exposing children with moderate levels of lead in early life, even <10 μg/dL has a long-term negative impact on cognitive development and educational attainment (Chandramouli et al. 2009; Magzamen et al. 2013). In the case of Arica, the children who were exposed to mineral waste containing heavy metals came from families with diverse levels of social vulnerability. It is necessary to assess using a similar methodology whether early life exposure to toxic waste could be related with other long-term effects to confirm the current results.
Acknowledgments

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