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Effects of lead, cadmium, arsenic, and mercury co-exposure on children's intelligence quotient in an industrialized area of southern China☆

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Exposure to metal(loid)s can lead to adverse effects on nervous system in children. However, little is known about the possible interaction effects of simultaneous exposure to multiple metal(loid)s on children's intelligence. In addition, relationship between blood lead concentrations (<100 μg/L) and the intelligence of children over 5 years needs further epidemiological evidence. We recruited 530 children aged 9–11 years, including 266 living in a town near an industrialized area and 264 from another town in the same city in South China as a reference. The levels of lead (Pb), cadmium (Cd), arsenic (As) and mercury (Hg) in blood (BPb, BCd, BAs, BHg) and urine (UPb, UCd, UAs, UHg) were assessed, as well as children's intelligence quotient (IQ). A significant decrease in IQ scores was identified in children from the industrialized town ($p < .05$), who had statistically higher geometric mean concentrations of BPb, BCd, UPb, UCd and UHg (65.89, 1.93, 4.04, 1.43 and 0.37 μg/L, respectively) compared with children from the reference town (37.21, 1.07, 2.14, 1.02 and 0.30 μg/L, respectively, $p < .05$). After adjusting confounders, only BPb had a significant negative association with IQ (B = −0.10, 95% confidence interval: −0.15 to −0.05, $p < .001$), which indicated that IQ decreased 0.10 points when BPb increased 1 μg/L. Significant negative interactions between BAs and BHg, positive interaction between UPb and UCd on IQ were observed ($p < .10$), and BPb <100 μg/L still negatively affected IQ ($p < .05$). Our findings suggest that although only BPb causes a decline in children's IQ when simultaneously exposed to these four metal(loid)s at relatively low levels, interactions between metal(loid)s on children's IQ should be paid special attention, and the reference standard in China of 100 μg/L BPb for children above 5 years old should be revised.

1. Introduction

Exposure to environmental metal(loid)s has raised worldwide concern. Arsenic (As), lead (Pb), mercury (Hg) and cadmium (Cd) rank the first, second, third, and seventh elements, respectively, in the Agency for Toxic Substances and Disease Registry (ATSDR) list posing the greatest potential threat to human health (ATSDR, 2013).

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These four metal(loid)s are neurotoxic and early exposure in children leads to potential predisposition to multisystem ailments, low intelligence quotient (IQ) and dysfunctional behavior over their lifetime (Rodriguez-Barranco et al., 2013; Sears et al., 2012). However, most previous studies have focused on the effects of a single metal(loid) (Ciesielski et al., 2012; Hamadani et al., 2010; Liu et al., 2013), while simultaneous chronic low-level exposure to these toxic metal(loid)s is more environmentally relevant. A few studies have reported the synergistic impact of two metal(loid)s at relatively low levels on children's intellectual function (Kim et al., 2009; Wasserman et al., 2011), and animal experiments indicated that a mixture of As, Cd, and Pb induced synergistic toxicity in astrocytes which subsequently led to behavioral dysfunction in developing rats (Rai et al., 2010). There is little information on the possible interaction effects of simultaneous exposure to Pb, Cd, As, and Hg at low concentrations on children's intelligence, which is a more realistic scenario in some industrial areas (de Burbure et al., 2005).

A blood Pb (BPb) level of 100 μg/L was set as a criterion of concern in China (NHFPC, 2006), however, recent studies have suggested that a BPb level below 100 μg/L may adversely impact children's IQ (Jusko et al., 2008; Lanphear et al., 2005; Surkan et al., 2007). The Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP) recommend 50 μg/L BPb as the reference value, and this value was set based on the 97.5th percentile of the population BPb level in children aged 1–5 years in the United States (ACCLPP, 2012). It is still questionable whether this value is suitable for children greater than 5 years and in other regions, especially in developing countries. Therefore, further epidemiological evidence is needed to describe whether the lead-associated decline in intelligence occurs at BPb concentrations below 100 μg/Lin children older than 5 years in developing countries (Liu et al., 2013).

S city, a traditional industrial city, is located in the north of Guangdong province, China, and has been dominated for decades by a large-scale nonferrous smelter and steel factories. Land in the proximity of the smelter has been seriously polluted, and investigations have indicated that Cd concentrations in farmland soil (2.46 mg/kg), Pb and Cd concentrations in rice (26.70 and 1.75 mg/kg, respectively) and vegetables (60.40 and 0.27 mg/kg, respectively) near the factories were above the Chinese government standards (GB15618, 1995, Cd in farmland soil 0.30 mg/kg; GB2762, 2012, Pb and Cd in rice 0.20 and 0.10 mg/kg, respectively; Pb and Cd in vegetables 0.30 and 0.20 mg/kg, respectively) (Cheng and Lu, 1984; Li et al., 2001a, 2001b; Lu, 1985). The large-scale nonferrous smelter plant has been preparing to close since 2012 and most of the workers have gone, but there are still many residents living in the area adjacent to the plants, who were probably exposed to these metal(loid)s due to the consumption of polluted rice and water.

Metal levels in blood or urine can be used as indicators of metal exposure, and different metals have their respective indicators in different matrices. Cadmium in blood (BCd) is widely viewed as a recent exposure indicator, while cadmium in urine (UCd) is viewed as a cumulative exposure biomarker (Lauwerys et al., 1994). Bone lead and the cumulative blood lead index (CBLI) are two useful biomarkers reflecting long-term or cumulative lead exposure, but the technology for detecting bone lead is not easily available and not well suited for routine measurements, and calculation of the CBLI requires a series of BPb levels recorded over a period of time (Nie et al., 2011; Roels et al., 1999). Therefore, a surrogate biomarker is used, such as BPb which reflects current or recent lead exposure, and a good relationship between BPb and bone lead has been reported (Börjesson et al., 1996). As for Hg and As, they could be in organic and inorganic forms, in human biomonitoring, the total mercury in urine (UHg),arsenic in urine (UAs), and Hg in blood (BHg) are often selected as biomarkers for cumulative exposure to metals due to their satisfactory correlations between exposure and metal-induced damage (Hata et al., 2016; Mary et al., 2014; Hughes, 2006; Roels et al., 1999). In the present study, in order to gain more information on internal metal exposure, we determined metal levels in both blood and urine. Thus, the objectives of the present study were to analyze the levels of BPb, BCd, BAs, BHg, UPb, UCd, UAs, and UHg, and evaluate the possible effects of co-exposure to these metal(loid)s on intelligence of school-aged children, and assess the relationship between BPb concentration under 100 μg/L and the intelligence of these children from an exposed industrial district and a non-exposed reference area in the same city using a cross-sectional study.

This investigation was part of a nationwide environmental priority pollutants monitoring and health hazards evaluation study at the Institute of Environmental Health and Related Products Safety, Chinese Center for Disease Control and Prevention (China CDC), which included eight research fields and our investigation was a subdivision to determine long-standing metal contamination from a nonferrous smelter and steel plants.

2. Materials and methods

2.1. Study population and recruitment

From November 2011 to February 2012, a cross-sectional study was conducted in two towns of S city. Children from the town where the smelter and steel plants were located were selected as the exposed group, and children from the other town in the same district were selected as the reference group. The reference town lies upstream and upwind of the plants with low metal(loid) occurrence as suggested by the data collected from Guangdong food contaminants risk monitoring in 2010–2011 conducted by Guangdong Provincial Center for Disease Control (CDC) (data not shown). Subjects living in these two areas had similar geographic and cultural conditions. In each area, we randomly selected a primary school and explained the project to the children and their parents or guardians in a meeting arranged by the schools, and invited them to participate in this study. In total, 266 children from the exposure area and 264 children from the reference area agreed to take part in the study. Their parents signed informed consents and completed questionnaires including demographic and socioeconomic information. The children who participated in this study were aged 9–11 years and had lived in the study area for at least 2 years. Children with a neurological disorder or physical illness were excluded from the study.

The study was approved by the ethic commission of the Institute of Environmental Health and Related Products Safety, China CDC.

2.2. Measurement of blood and urinary samples

Polypropylene containers for venous blood and urine samples were supplied by the Institute of Environmental Health and Related Products Safety, China CDC. Children were provided with polypropylene containers to collect first morning spot urine samples the day before the intelligence test. Trained nurses collected blood samples from the children on the same day as the intelligence test in the school. All biological samples were refrigerated at −4 °C until transported to the laboratory, and stored at −20 °C until analysis.

According to Environmental Protection Agency (EPA) 200.8 method (EPA, 2012), the levels of BPb, BCd, BAs, BHg, UPb, UCd, UAs, and UHg were analyzed using an Agilent 7500C inductively coupled plasma - mass spectrometry (ICP-MS) (Agilent, Palo Alto, CA, USA). The limits of detection (LOD), linear range and correlation coefficient, recovery and standard deviation were evaluated to validate the accuracy and precision of the analytical methods. The specific ICP-MS parameters are presented in the Supplementary Material. The LOD for BPb, BCd, BAs and BHg were 2.0, 0.03, 0.1, and 0.03 μg/L, respectively, and the LOD for UPb, UCd, UAs and UHg were 0.5, 0.1, 0.2, and 0.1 μg/L, respectively. There were thirteen samples in the non-exposed group and three samples in the exposed group in which UHg values were below the LOD, and three samples in the non-exposed group in which UPb values were below the LOD, which were replaced by one half of the LOD (Sun et al., 2015).

2.3. Measurement of children's IQ scores

Children's intelligence was tested following the method of the Combined Raven's Test in China which was revised in 1997 for the second time (CRT-C_2). This method is based on the Raven's Standard Progressive Matrices (SPM) and Color Progressive Matrices (CPM) for fluid intelligence and is widely used in China after correction for cultural, ethnic, and language differences (Wang et al., 2007). The CRT-C_2 test included 72 questions in six groups which were related to the CPM groups A, A_B, and B, and the SPM groups C, D, and E in the original Raven scales. This test was a nonverbal IQ test and was close to the functioning scales in the WISC-III (Wechsler Intelligence Scale-3rdEdition). The CRT-C_2 method was applied in both towns by the same three public health physicians from Guangdong CDC, all of which were trained and certified by China CDC. The test was firstly applied in the reference town, then after a week, applied in the exposed town. The children's IQ scores were classified into the following seven categories: ≤69, low intelligence; 70–79, marginal intelligence; 80–89, below medium; 90–109, medium; 110–119, above medium; 120–129, good; and ≥130, excellent.

2.4. Statistical analysis

Geometric means and 95% confidence interval (CI) were used to describe the levels of BPb, BCd, BAs, BHg, UPb, UCd, UAs, and UHg, and the arithmetic means and standard deviations were used to describe the children's IQ scores. According to the Kolmogor–Smirnov test, distribution of the children's IQ scores was normal, thus one-way analysis of variance (ANOVA) and the student's t-test were used to compare differences in IQ scores in a stratified analysis, while the Mann–Whitney test and the Kruskal Wallis test were performed for metal(loid) exposure variables with non-normal distribution.

In addition to neurotoxic exposure, children's IQ can also be influenced by genetic, familial, education and nonfamilial factors (Mink et al., 2004). Hernán and coworkers considered that prior subject matter knowledge was a prerequisite for confounding evaluation (Hernán et al., 2002). Based on this and analysis of the correlations between the potential confounders and metal(loid)s or IQ of children in our study (Table S1 in the Supplementary Material, "S" represents figures and tables in the Supplementary Material thereafter), confounders were first identified and then appropriately adjusted. The confounders were as follows: children's age (Tong and Liu, 2001) and sex (Canfield et al., 2003; Li et al., 2016; Liop et al., 2013), passive smoking at home (Galazyn-Sidorczuk et al., 2008; Herrmann et al., 2008), annual family income, education and occupation of parents (Hanscombe et al., 2012; Tong et al., 2007).

Linear regression analysis was performed to assess the relationship between children's IQ scores and metal(loid) exposure levels, where blood and urine metal(loid) levels were considered independent variables. First univariable linear regression analysis of each metal(loid) unadjusted for the confounders was performed, then multivariable adjusted linear regression models by enter method were carried out. A p-value of 0.05 was considered statistically significant for all analyses (including data distribution test, metal(loid)s or IQ differences in stratified analysis, relations between metal(loid) exposure and IQ). Multivariable adjusted linear regression models were carried out to evaluate possible interactions between exposure levels of metal(loid)s (A p-value = .10 was considered significant). Data were analyzed by IBM SPSS Statistics 20.0 (Provided by China CDC).

3. Results

3.1. Characteristics of the participants

Socio-demographic characteristics of the children included in the study are shown in Table 1. The final sample included 266 exposed and 264 non-exposed children. The number of girls and boys was almost equal and no significant differences in the proportion of girls and boys were observed between the two groups ($p = .54$). No significant differences in children's age, mother's age and father's age were observed between the two groups. The average age of the parents in the two groups was less than 40 years. Statistically significant differences in occupation and education of parents and annual family income were observed between the two groups. More parents in the exposed group had received education

Table 1
Socio–demographic and birth characteristics of children included in the study.

	Comparison group		Exposed group		p
	n	(%)	n	(%)	
Total	264	(100)	266	(100)	
Sex					
Boys	133	(50.4)	127	(47.7)	
Girls	131	(49.6)	139	(52.3)	0.54
Children's age	10.0 ± 0.8	9.9 ± 0.8	0.13[a]		
Mother's age	36.5 ± 4.6	36.7 ± 3.8	0.77[a]		
Father's age	38.8 ± 4.5	38.9 ± 4.5	0.70[a]		
Mother's occupation					
Unemployed	20	(8.9)	45	(18.9)	
Farmers	116	(51.8)	61	(25.6)	
Employed in steel	15	(6.7)	22	(9.2)	
Employed in others	73	(32.6)	110	(46.3)	<0.001**
Mother's education					
Middle school or lower	208	(83.9)	177	(69.7)	
High school	26	(10.5)	50	(19.7)	
College or above	14	(14.0)	27	(10.6)	0.001*
Father's occupation					
Unemployed	6	(2.6)	10	(4.3)	
Farmers	127	(55.9)	65	(28.3)	
Employed in steel	18	(7.9)	37	(16.1)	
Employed in others	76	(33.6)	118	(51.3)	<0.001**
Father's education					
Middle school or lower	191	(77.3)	148	(58.3)	
High school	36	(14.6)	65	(25.6)	
College or above	20	(8.1)	41	(16.1)	<0.001**
Annual family income (RMB)					
≤30,000	167	(68.2)	114	(46.7)	
30,000–100,000	68	(27.8)	111	(45.5)	
≥100,000	10	(4.1)	19	(7.8)	<0.001**
Passive smoking at home					
Yes	88	(35.9)	79	(31.6)	
No	157	(64.1)	171	(68.4)	0.342
Premature birth					
Yes	12	(4.8)	10	(3.9)	
No	237	(95.2)	245	(96.1)	0.62
Delivery method					
Natural birth	199	(80.6)	206	(81.4)	
Caesarean	48	(19.4)	47	(18.6)	0.97

Note: The age data are presented as mean ± standard deviation. [a] Student's t–test, the others are Chi–square test.$^{*}p < .05$, $^{**}p < .001$.

at high school level and above than the non-exposed group (mother 30.3% vs. 24.5%; father 41.7% vs. 22.7%), and had a higher annual family income compared with the non-exposed group. More parents in the non-exposed group (greater than 50%) were farmers compared with parents in the exposed group (less than 30%). Only a small proportion of parents (approximately 10%) in the two groups worked in the smelter and steel plants, as the large-scale smelter was preparing to close.

3.2. Blood and urine metal(loid)s levels

Levels of the four metal(loid)s in the blood and urine of children in the two groups are shown in Table 2. In the non-exposed group, the geometric means of BPb, BCd, BAs, and BHg were 37.21, 1.07, 1.09, and 1.61 μg/L, respectively, and the geometric means of UPb, UCd, UAs, and UHg were 2.14, 1.02, 29.86, and 0.30 μg/L, respectively. The geometric means of BPb, BCd, BAs, and BHg in the exposed group were 65.89, 1.93, 1.19, and 1.55 μg/L, respectively, with the geometric means of UPb, UCd, UAs, and UHg were 4.04, 1.43, 29.29, and 0.37 μg/L, respectively. Comparatively, exposed children had statistically higher concentrations of BPb, BCd, UPb, UCd and UHg than non-exposed children.

3.3. Children's IQ

Children in the exposed group had significantly lower IQ scores (mean ± SD, 103.38 ± 10.76) than children (mean ± SD, 106.23 ± 12.84) in the non-exposed group ($p = .006$) (Table 2). Furthermore, the Chi-square test showed that the distribution of children's IQ scores was significantly different between the groups ($p = .005$). In the non-exposed group, the proportions were as follows: 54.4% had an IQ score of 90–109 (medium), 21.2% had an IQ score of 110–119 (above medium), 10.8% had an IQ score of 120–129 (good), and 5% had an IQ score ≥130 (excellent). In the exposed group, the proportion of children with a medium IQ score increased to 65.4%, and the proportions with an above medium, good, and excellent IQ score decreased to 19.4%, 6.5%, and 0.4%, respectively.

3.4. Metal(loid) exposure levels and children's IQ

Using univariable linear regression analysis without adjusting for confounders, only BPb was significantly inversely associated with children's IQ (B = −0.09, $p < .001$) and BCd was possibly inversely associated with children's IQ (B = −0.63, $p = .05$) (Table S2), while no statistically significant associations were found between the other metal(loid)s in blood and IQ scores, or between the four metal(loid)s in urine and IQ scores. When the four metal(loid)s in blood were all entered into multivariable linear regression analysis without adjusting for confounders, only BPb remained significantly negatively associated with IQ (B = −0.09, $p < .001$) (Table 3). After adjusting confounders including children's age and sex, passive smoking at home, annual family income, parents' education and occupation, multivariable adjusted linear regression analysis showed that still only BPb was significantly negatively associated with IQ (B = −0.10, 95% CI: −0.15 to −0.05, $p < .001$). We also found that children's IQ was significantly positively associated with mother's high school education (B = 4.10, 95% CI: 0.87 to 7.33, $p = .013$), and an annual family income of ≥100,000 RMB (B = 5.77, 95% CI: 1.20 to 10.34, $p = .014$), respectively (Table 3). When the four metal(loid)s in urine were all entered into multivariable linear regression model, whether adjusting the confounders or not, no statistical significant

Table 3
Relationships between metal(loid)s in blood and IQ.

Factors	IQ		
	B (95%CI)	SE	p
Unadjusted for confounders			
BPb	−0.09 (−0.13, −0.04)	0.02	<.001**
BCd	−0.05 (−0.74, 0.64)	0.35	.887
BAs	−0.55 (−1.68, 0.64)	0.59	.378
BHg	0.35 (−0.87, 1.58)	0.63	.571
$\triangle R^2$	0.03		
Adjusted for confounders			
BPb	−0.10(−0.15, −0.05)	0.03	<.001**
Children's age	−1.61 (−2.89, −0.34)	0.65	.013*
Mother's education			
Middle school or lower	Ref		
High school	4.10 (0.87, 7.33)	1.64	.013*
College school or above	−1.20(−6.27, 3.87)	2.58	.643
Annual family income (RMB)			
≤30,000	Ref		
30,000–100,000	1.65(−0.76, 4.05)	1.23	.180
≥100,000	5.77 (1.20, 10.34)	2.33	.014*
Children's sex	−0.78(−2.90, 1.32)	1.07	.463
Father's education			
Middle school or lower	Ref		
High school	−0.78(−3.58, 2.03)	1.43	.587
College school or above	1.81(−2.63, 6.26)	2.26	.423
Mother's occupation			
Famers	Ref		
Workers in steel	1.87(−2.96, 6.71)	2.46	.447
Other workers	1.28(−1.79, 4.34)	1.56	.415
Father's occupation			
Famers	Ref		
Workers in steel	2.34(−1.92, 6.61)	2.17	.280
Other workers	1.63(−1.52, 4.78)	1.60	.310
Passive smoking at home	−1.15(−3.34, 1.04)	1.12	.310
$\triangle R^2$	0.08		

Note: 1.Adjusted confounders included children's age and sex, passive smoking at home, annual family income, parents' education and occupation. 2.$\triangle R^2$ represents adjusted R square.**$p < .001$, *$p < .05$.

Table 2
Levels of metal(loid)s in blood and urine by groups [GM(95%CI), μg/L] and IQ scores.

	Comparison group (n = 250)	Exposed group (n = 253)	p[a]
BPb	37.21 (35.70–38.77)	65.89 (62.98–68.91)	<.001**
BCd	1.07 (1.00–1.14)	1.93 (1.78–2.10)	<.001**
BAs	1.09 (1.04–1.14)	1.19 (1.12–1.28)	.096
BHg	1.61 (1.53–1.69)	1.55 (1.47–1.63)	.609
UPb	2.14 (1.98–2.30)	4.04 (3.79–4.31)	<.01**
UCd	1.02 (0.93–1.12)	1.43 (1.31–1.57)	<.01**
UAs	29.86 (27.62–32.29)	29.29 (26.97–31.82)	.218
UHg	0.30 (0.28–0.33)	0.37 (0.34–0.40)	.01*
IQ [n($\bar{x}$±s)]	259 (106.23 ± 12.84)	263 (103.38 ± 10.76)	.006[b]*

GM represents geometric mean.*$p < .05$, **$p < .001$.

[a] Mann–Whitney U test between the non-exposed and exposed groups, with the exception of IQ.

[b] Student's t-test.

associations between these metal(loid)s and IQ scores were observed (Table S3).

To estimate the magnitude of the negative association between BPb and IQ scores, based on the regression coefficient for BPb in the model adjusting for confounders, we derived the decrease in IQ scores when Pb exposure increased from the lowest to the highest BPb quartile. When comparing the lowest (<35.65 μg/L) and highest (>70.65 μg/L) BPb quartiles, children's IQ scores decreased by 3.5 points.

3.5. Interactions between Metal(loid)s on children's IQ

Interactions between metal(loid)s on children's IQ were evaluated using two metal(loid) variables in continuous scale in multivariable linear regression model (centering metal(loid) variables and interaction terms) after adjusting confounders (Xie, 2010). If the interaction term was significant, metal(loid)s were dichotomized in the median and stratified multivariable linear regression models after adjusting confounders were performed. We found that there were significantly negative interaction between BAs and BHg (B = −0.11, 95% CI: −0.18 to −0.05, $p = .091$) (Table 4) and positive interaction between UPb and UCd (B = 0.10, 95% CI: −0.01 to 0.20, $p = .081$) (Table 5), and no significant interactions between other metal(loid)s were found. Furtherly, changes in the direction of the estimated regression coefficient at different layer were observed in interactions between BAs and BHg (from −0.50 to 0.85, from −0.23 to 0.95) (Table S5), UPb and UCd (from −0.70 to 0.10; from −0.06 to 0.27) (Table S6).

3.6. Relation between BPb below 100 μg/L and children's IQ

We further assessed the relationship between BPb below 100 μg/L (excluding 27 samples above 100 μg/L, ranging from 100.20 to 160.40 μg/L) and children's IQ. After adjusting the same confounders, multivariable adjusted linear regression also indicated that of the four metal(loid)s only BPb was significantly negatively associated with IQ (B = −0.10, 95%CI: −0.16 to −0.04, $p = .002$) (Table S4). Children's IQ scores decreased by 3.23 points when the lowest (<34.68 μg/L) and the highest (>67.53 μg/L) BPb quartiles were compared based on the estimated regression coefficient for BPb in the model. Furthermore, in order to determine a possible BPb level (below 100 μg/L) above which children's IQ was adversely affected, the mean IQ values between the BPb below 100 μg/L quartile groups were compared using ANOVA taking into consideration the following confounders: children's age (using the ANOVA test), mother's education (using the Chi-square test), and annual family income (using the Chi-square and ANOVA tests). These three confounders were chosen based on the results of the regression model (BPb below 100 μg/L, Table S4). The test showed that only children in the highest quartile (BPb > 67.53 μg/L) had a significant decline in IQ scores ($p < .001$) when compared with children in the lowest quartile as illustrated in Fig. 1.

Table 4
Interactions between blood metal(loid)s on IQ.

Metal(loid)s	IQ		
	B(95%CI)	SE	*P*
Interaction between Pb and Cd			
BPb	−0.10(−0.15, −0.05)	0.03	.001**
BCd	0.08(−0.08, 0.12)	0.41	.836
BPb × BCd	0.007(−0.01, 0.03)	0.01	.409
Interaction between Pb and As			
BPb	−0.10 (−0.13, −0.05)	0.03	.001**
BAs	−0.63(−1.88, 0.63)	0.64	.327
BPb × BAs	−0.07(−0.05, 0.04)	0.02	.758
Interaction between Pb and Hg			
BPb	−0.10(−0.14, −0.05)	0.02	.001**
BHg	−0.30(0.09, −0.09)	0.62	.632
BPb × BHg	0.04(−0.01, 0.09)	0.03	.163
Interaction between Cd and As			
BCd	−0.48(−1.13, 0.18)	0.33	.151
BAs	−0.93(−2.18, 0.32)	0.64	.145
BCd × BAs	0.15(−0.51, 0.81)	0.33	.649
Interaction between Cd and Hg			
BCd	−0.60(−1.24, 0.05)	0.33	.070*
BHg	0.34(−0.94, 1.61)	0.65	.604
BCd × BHg	0.37(−0.57, 1.31)	0.48	.442
Interaction between As and Hg			
BAs	−1.16(−2.34, 0.02)	0.60	.053
BHg	−0.04(−1.4, 1.29)	0.68	.955
BAs × BHg	−0.11(−0.18, −0.05)	0.41	.091*

Note: Multiple linear regression analysis were performed with adjusting children's age and gender, passive smoking at home, parents' education and occupation, yearly family income. **$p < .001$, *$p < .10$.

Table 5
Interactions between urine metal(loid)s on IQ.

Metal(loid)s	IQ		
	B(95%CI)	SE	*P*
Interaction between Pb and Cd			
UPb	−0.44(−0.96, 0.09)	0.27	.101
UCd	−0.04(−0.96, 0.88)	0.47	.935
UPb × UCd	0.10(−0.01, 0.20)	0.06	.081*
Interaction between Pb and As			
UPb	−0.20 (−0.63, 0.24)	0.22	.370
UAs	−0.02(−0.05, 0.02)	0.02	.404
UPb × BAs	0.01(−0.01, 0.02)	0.01	.536
Interaction between Pb and Hg			
UPb	−0.21(−0.64, 0.22)	0.22	.341
UHg	−0.87(−2.18, 0.32)	0.85	.304
UPb × UHg	0.34(−0.17, 0.84)	0.26	.188
Interaction between Cd and As			
UCd	−0.03(−0.79, 0.73)	0.39	.938
UAs	−0.02(−0.06, 0.01)	0.02	.178
UCd × UAs	0.01(−0.01, 0.03)	0.01	.169
Interaction between Cd and Hg			
UCd	−0.02(−0.76, 0.72)	0.38	.954
UHg	−0.49(−2.26, 1.28)	0.90	.588
UCd × UHg	0.19(−0.41, 0.79)	0.31	.539
Interaction between As and Hg			
UAs	−0.02(−2.34, 0.02)	0.02	.295
UHg	0.55(−1.4, 1.29)	0.62	.373
UAs × UHg	0.07(−0.02, 0.16)	0.05	.145

Note: Multiple linear regression analysis were performed with adjusting children's age and gender, passive smoking at home, parents' education and occupation, yearly family income. *$p < .10$.

4. Discussion and conclusions

In this study we found that children who lived near the industrial area and were exposed to toxic metal(loid)s had significantly lower IQ scores than non-exposed children in the same city (mean 103.38 vs 106.23). Multivariable adjusted linear regression analysis after adjustment for some confounders showed that only BPb was significantly inversely associated with children's IQ scores (B = −0.10, 95% CI: −0.15 to −0.05, $p < .001$) following simultaneous exposure to these relatively low levels of Pb, Cd, As and Hg. BPb levels lower than 100 μg/L also had a significant negative effect on children's IQ in this study (B = −0.10, 95% CI: −0.16 to −0.04, $p = .002$).

Childhood exposure to a combination of metal(loid)s is an important public health concern, especially in developing countries (Liu et al., 2013). In this study, we described the metal(loid) levels in blood and urine in school-aged children living in an area where

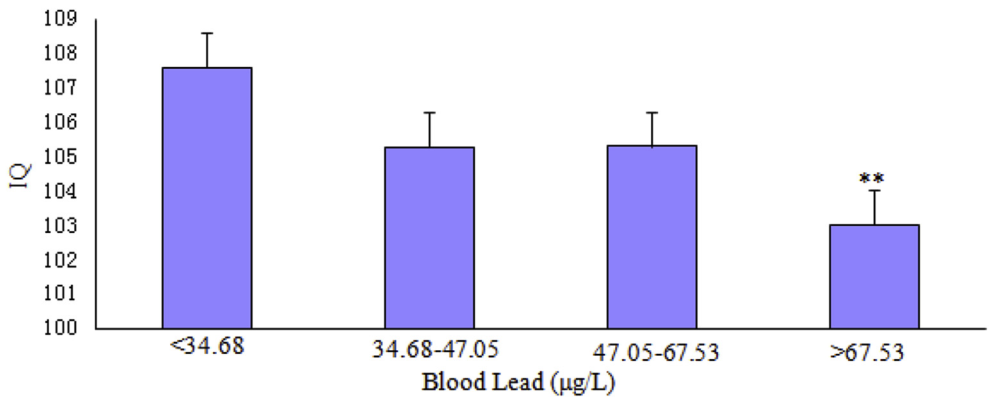

Fig. 1. Mean IQ scores of children with BPb below 100 μg/L divided into quartiles of BPb concentration after considering children's age, mother's education, annual family income. Statistically significant difference from first quartile.$^{**}p < .001$.

nonferrous smelters were located. The exposed children had higher metal(loid) levels both in blood and urine than non-exposed children. Compared with the general population of children in China (Ding et al., 2014), the geometric means of children's BPb, BCd, UPb and UCd in this study surpassed (range 2–10-fold higher, Table S7) those in the general population of children. Furthermore, compared with some developed countries, the children included in this study were exposed to high levels of environmental metal(loid)s. For example, human biomonitoring reports from Germany showed that in children aged 3–14 years, the 95% population reference values for BPb, BCd, and BHg were 35, <0.3 and 0.8 μg/L, respectively, and for UAs, UCd, and UHg were 15, 0.2 and 0.4 μg/L, respectively (Schulz et al., 2012). A recent Japanese biomonitoring study of children aged 9–10 years reported that the geometric means of BCd and UCd were 0.34 and 0.21 μg/L, respectively, and was 9.6 μg/L for BPb (Ilmiawati et al., 2015). Therefore, although the local government has carried out some measures to prevent heavy metal(loid) pollution, there is more work to be done to protect children from environmental metal(loid) contamination.

Exposed children had significantly lower IQ scores than non-exposed children (mean 103.38 vs 106.23), only BPb was significantly negatively associated with IQ ($B = -0.10$, $p < .001$) in this study. But in the real environment, children were often exposed to mixtures of these metal(loid)s. So their possible interactions on children's intelligence aroused much attention. Animal experiments have indicated that a mixture of Pb, Cd and As could induce synergistic toxicity in astrocytes and may cause behavioral dysfunction in developing Wistar rats (Rai et al., 2010). And some researchers reported that there were interaction effects between BAs and blood manganese (BMn) (Wasserman et al., 2011), BPb and BMn (Kim et al., 2009) on children's intelligence. However, there was little epidemiologic evidence for interactions between these four metal(loid)s on children's intelligence. In our study analysis of the interactions between metal(loid)s with regard to children's IQ showed that there were significant negative interaction between BAs and BHg ($B = -0.11$, $p = .091$), positive interaction between UPb and UCd ($B = 0.10$, $p = .081$) at these relatively low level of metal(loid)s. This suggested that interactions between metal(loid)s on children's IQ should paid much more attention, and synergistic and antagonistic effects between metal(loid)s could coexist at the same time when children were exposed to mixtures of metal(loid)s. Thus, the results of this study not only provide very important clues for the further study, but assist the government in making much more effective policies and measures for the control of metal(loid)s pollution when considering synergistic or antagonistic effects between metal(loid)s.

Further analysis of BPb below 100 μg/L indicated that the children's IQ scores decreased by approximately 3.23 points from the highest BPb quartile to the lowest. These findings were similar to those in the ACCLPP report, in which an increase in BPb from 10 to 40 μg/L was associated with a change in mean IQ of approximately −2.3 to −5.2 IQ points, with a best estimate of −3.7 IQ points. In addition, the ANOVA test was carried out to determine significant differences in children's IQ scores at BPb levels below 100 μg/L and it was shown that IQ score decreased significantly at the highest quartile (BPb >67.53 μg/L) when compared with the lowest quartile ($p < .001$). Furthermore, in this study children's current BPb concentrations were measured concurrently with children's IQ, which could well reflect association between Pb exposure and children's IQ. Indeed some researcher reported that children's IQ correlated better with their current BPb level than with peak levels determined at an earlier age in a cross-sectional study (Carpenter, 2005; Chen et al., 2005). Therefore, our study results have not only extended previous evidence that even a BPb level below 100 μg/L can have an adverse effect on a child's IQ (Barbosa et al., 2005; Canfield et al., 2003), but also provide important evidence to support a negative relationship between BPb exposure at low level and IQ in children aged more than 5 years, as the new BPb reference value of 50 μg/L (ACCLPP) is only for children aged 1–5 years. However, the BPb reference value for all children is still 100 μg/L in China, thus our study results provide strong evidence for a revision of this reference level.

With regard to Cd, this metal has different recommended reference values. The American Conference of Governmental Industrial Hygienists state a maximum recommended human BCd value of 5 μg/L (ACGIH, 2007), and the European Food Safety Authority (EFSA, 2009) and the World Health Organization/Food and Agriculture Organization of the United Nation (World Health Organization/Food and Agriculture Organization of the United Nation, 2011) recommend a UCd reference level of 1 μg/L. The German Human Biomonitoring Commission defined the reference value of UCd as greater than 2 μg/L, and above this level there is an increased risk of adverse health effects in children (Schulz et al., 2012). However, recent studies have suggested that even UCd levels below 1 μg/L can impair neurodevelopment in children (Ciesielski et al., 2012; Rodriguez-Barranco et al., 2014). In our study, BCd and UCd concentrations in both groups were below 2 μg/L (BCd 1.07 μg/L and UCd 1.02 μg/L in the non-exposed; BCd 1.93 μg/L and UCd 1.43 μg/L in the exposed). Although linear regression analysis showed a possible negative association between BCd and IQ ($B = -0.63$, $p = .05$), no significant association was observed in the adjusted linear regression analysis. One possible explanation was that Cd exposure levels did not cause significant neuropsychological effects in the studied children, and more cohort studies with larger sample sizes are necessary to define the potential effects of low level environmental Cd exposure on neurodevelopment in children.

With regard to Hg and As, the German Human Biomonitoring Commission stated that BHg below 5 μg/L and UHg below 7 μg/L would not cause adverse health effects (Schulz et al., 2012), and UAs in children should not exceed 50 μg/L according to ATSDR (ATSDR, 2000). No significant relationships between Hg or As exposure levels and children's IQ were observed in our study. Besides, for Hg and As, they could be in different species, such as methyl-Hg, which could have different kinds of toxicity (Björnberg et al., 2003). But in our study, there were no significant differences of BAs, BHg, UAs, UHg between reference and exposed children group, also, no significant relations between these two metal(loid)s and IQ, what's more, the levels of BAs, BHg, UAs, UHg in these children were relatively low. So in our study, the total BAs, BHg, UAs, UHg were used.

This study was a cross-sectional investigation. So one of the limitations was that confounder analyses were not enough. Although some important confounders were analyzed, other potential confounders, such as parent's marital status and IQ, were not considered. More research is needed to confirm possible interactions between metal(loid)s on children's IQ, but we provided important clues. In addition, except metals in blood and urine, metals in other biological samples can also be good biomarkers, such as hair or nail As (Marchiset-Ferlay et al., 2012). So in the further study, more biomarkers were considered to be detected to more completely assess effects of environmental metals exposure on children's neurodevelopment.

In conclusion, this study demonstrates that only BPb was negatively associated with school-aged children's IQ at this relatively low level of environmental heavy metal(loid)s pollution in an industrial area and added weight to the evidence that BPb below 100 μg/L can also cause adverse effects on children's IQ. Interactions between metal(loid)s provide important clues for further studies on the interaction effects of simultaneous metal(loid)s exposure on children's IQ. These findings are important for the local government to establish more effective policies for the prevention and control of metal(loid)s pollution.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.envpol.2017.12.044.

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