RESEARCH ARTICLE

Effects of lead and cadmium exposure from electronic waste on child physical growth

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Abstract Many studies indicate that lead (Pb) and cadmium (Cd) exposure may alter bone development through both direct and indirect mechanisms, increasing the risk of osteoporosis later in life. The aim of this study was to investigate the association between Pb and Cd exposure, physical growth, and bone and calcium metabolism in children of an electronic waste (e-waste) processing area. We recruited 246 children (3–8 years) in a kindergarten located in Guiyu, China. Blood lead levels (BLLs) and blood cadmium levels (BCLs) of recruited children were measured as biomarkers for exposure. Serum calcium, osteocalcin, bone alkaline phosphatase, and urinary deoxypyridinoline were used as biomarkers for bone and calcium metabolism. Physical indexes such as height, weight, and head and chest circumference were also measured. The mean values of BLLs and BCLs obtained were 7.30 μg/dL and 0.69 μg/L, respectively. The average of BCLs increased with age. In multiple linear regression analysis, BLLs were negatively correlated with both height and weight, and positively correlated with bone resorption biomarkers. Neither bone nor calcium metabolic biomarkers showed significant correlation with cadmium. Childhood lead exposure affected both physical development and increased bone resorption of children in Guiyu. Primitive e-waste recycling may threaten the health of children with elevated BLL which may eventually cause adult osteoporosis.

Keywords Electronic waste (e-waste) · Lead · Cadmium · Children · Physical growth · Bone biomarker · Osteoporosis

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Background, aim, and scope

Lead (Pb) and cadmium (Cd) are significant industrial and environmental pollutants, and their ubiquity in the environment and bioaccumulation in organisms have led to a variety of adverse effects in mammals. The neurotoxicity of Pb on children is widely studied and well documented (Olympio et al. 2009; Finkelstein et al. 1998; Zahran et al. 2009) as well as its association with other diseases (Moncrieff et al. 1964). It has also been confirmed that childhood exposure to Pb can cause bone demineralization and damage, thus influencing a child's growth. Moreover, bone carries nearly 95 % of the total Pb burden in the individual body (Barry and Mossman 1970; Kim et al. 1995). Long half-life of lead in bone provides an index of cumulative exposure over decades. The storage and release of Pb follow the general physiology of bone calcium with similar kinetics, and therefore have the potential to interfere

with bone and calcium metabolism. Recent epidemiological data and experimental works showed that effects of Pb on bone cell functions could persist for a lifetime eventually leading to osteoporosis and osteopenia (Barry 1975; Goyer et al. 1994; Min et al. 2008; Shen et al. 2001).

Furthermore, high environmental Cd exposure is also associated with bone damage (osteoporosis and osteomalacia). This type of bone damage has been described in women affected by the Itai-Itai disease. Studies also indicated that even relatively low exposure concentration levels may produce adverse effects on the skeleton, such as low bone mineral density (BMD) (Alfvén et al. 2000; Järup and Alfvén 2004; Sughis et al. 2011).

Despite considerable research on bone damage caused by Pb and Cd toxicity, the mechanisms are still not very well characterized. Many studies described the direct cellular toxic effect of Pb and Cd on osteoblast and osteoclast function and the indirect adverse renal effects of Pb and Cd. Reports have shown that Pb or Cd can act directly on bone cells and cause decreases in bone formation and increases in bone resorption, independent of their effects on the kidney, intestine, or circulating hormone concentrations (Ohta et al. 2002; Schutte et al. 2008). Both metals are also nephrotoxic (Alfvén et al. 2002; De Burbure et al. 2006), and their low-level chronic exposure increases the excretion of low molecular weight proteins and lysosomal proteins, impairs kidney function, inhibits the uptake of dietary vitamins and calcium, and disturbs vitamin D metabolism (Chalkley et al. 1998; Rosen et al. 1980). The three most likely mechanisms by which these metals might contribute to the development of osteoporosis include alteration of (1) peak bone mass, (2) the rate of bone resorption in an older person, and/or (3) alteration of the structural integrity of the bone (Goyer et al. 1994). Although there is good support for retardation of endochondral bone growth by lead, long-term consequences of this retardation on peak skeletal mass remain yet to be established. Studies on the effects of long-term Pb and Cd exposure on bone damage to either support or to eliminate a role for Pb and Cd in the pathogenesis of osteoporosis are needed.

Guiyu is an electronic waste-recycling site in southeast China. The processes and techniques used to recycle electrical waste in Guiyu are primitive. Various hazardous heavy metals are released into the environment threatening the health of local residents. Several studies conducted in Guiyu have reported the high levels of toxic heavy metals and organic contaminants in samples of dust, soil, river sediment, surface water, and groundwater of Guiyu (Deng et al. 2006; Wong et al. 2007; Yu et al. 2006). Our previous studies showed that neonates and children of Guiyu had significantly higher blood lead levels (BLLs) and blood cadmium levels (BCLs) than those from Chendian (a neighboring town) and other suburban areas (Guo et al. 2010;

Huo et al. 2007; Li et al. 2008, 2011; Liu et al. 2011; Zheng et al. 2008, 2012). The aim of our present study is to examine the relationship between lead and cadmium exposure and their effects on bone development in children in e-waste recycling area.

Materials and methods

Study population and sample collection

We recruited 246 children aged 3–8 from a village kindergarten in Guiyu. Unhealthy children or those on medication were excluded. After informed consent was obtained from their parents or guardians, blood and urine samples were collected by well-trained nurses, placed on ice, transported to the laboratory, and stored at −20 °C until analysis. Physical indexes (height and weight, and head and chest circumference) were also measured. To avoid contamination, all plastic tubes and containers used for urine collection were pre-washed, soaked in dilute HNO_3, and rinsed with deionized water.

A self-designed questionnaire was used to conduct a survey of parents or guardians. The questionnaire addressed factors that might influence a child's BLLs or BCLs, including questions relating to residence, physical activity, dieting habits, nutrition, whether the parent's occupation was related to e-waste processing, and the parent's education level and socioeconomic status. A medical and health history was also taken into consideration.

Measurement of blood Pb and Cd

Levels of Pb and Cd in the blood were used to assess exposure. Before analysis, 100-μL blood samples were put into tubes, and 900 μL of 0.5 % nitric acid (for blood cadmium, 2 % HNO_3) was added, vortexed, and subsequently digested for 10 min. The mixture was then used for lead determination. Unlike typical lead determinations, the solution had to be centrifuged for 10 min at 2,000 rpm after digestion to separate the supernatant for Cd analysis.

Both metals were determined by graphite furnace atomic absorption spectrophotometry (Jena Zenit 650, Germany), which consists of an autosampler (MPE60), with an injection volume set at 20 μL. The main parameters used for lead determination were: a wavelength of 283.3 nm, a lamp current of 4.0 mA, a slit width of 0.8 nm, drying at 90, 105, and 120 °C, ashing at 600 °C, and atomization at 1,500 °C. The standard calibration curve was plotted by the six working standard solutions which were prepared by stock Pb standard solutions diluted by nitric acid and added matrix modifier mixed with human blood. The linear correlation coefficient of the lead standard calibration curve was

0.9916. Accuracy of the method was controlled by recoveries between 95 and 107 %. The parameters for Cd analysis were: a wavelength of 228.8 nm, a current of 2.0 mA, a slit width of 1.2 nm, drying at 90, 105, and 120 °C, ashing at 300 °C, and atomization at 1,300 °C. The linear correlation coefficient of the Cd standard calibration curve was 0.9990. The recoveries for this method were 100–103 %, which were also from spiked blood samples.

Biochemical measurements

The following biochemical markers which relate to the bone metabolism were measured: serum osteocalcin, bone alkaline phosphatase (bALP), calcium (Ca), and urine deoxypyridinoline (uDPD). The immunoassays for osteocalcin, bALP, and uDPD were performed using a commercial ELISA kit (Sun Biomedical Technology, Beijing, China) and an ELISA automatic microplate reader (BIO-TEK, USA). Analysis of the sample solution was repeated to confirm the method's precision. The CVs were <13 % for osteocalcin, <9 % for U-DPD, and <6 % for bALP. Urinary creatinine was determined by a colorimetric assay, using commercially available kit (Nanjing, Jiancheng, China). uDPD was then adjusted to urinary creatinine to account for differences in dilution of the urine. The total serum Ca was determined by compleximetry (Fosun Long March Medical Science Company, Shanghai, China) and an automatic biochemistry analyzer (Beckman DXC 800, USA).

Statistical analysis

For database management and statistical analysis, we used SPSS 13.0. We expressed the central tendency and the spread of variables by the mean or the medium and the 5th to 95th percentile interval. Spearman rank correlation (rs) was used to assess any univariate associations. Mann–Whitney U test, t test, and Chi-square test were used to compare the covariates between subjects by cumulative Pb exposure status (i.e., low vs. high). All p values were derived with a two-sided hypothesis.

Multiple linear regression models were used to analyze any association between exposure and physical growth. For each of the three models, the physical growth variable was evaluated in relation to Pb, Cd, and confounding factors (age and sex of the children). Not all variables were included in one model because physical growth variables had a high degree of collinearity. For each model, height, weight, or BMI was the dependent variable and age, sex, BLLs, and BCLs were the independent variables.

Associations between biomarkers of effect and exposure were evaluated using multiple linear regressions. We indentified covariates by a stepwise regression procedure with the p values for variables to enter and to stay in the model set at

0.15. Covariates considered for entry in the model were age, gender, body mass index, use of supplements (calcium and/or vitamin D), and socioeconomic status.

Results

Characteristics of the study population regarding sex, age, blood cadmium, blood lead, and bone biomarkers are presented in Table 1. In the first evaluation, we assessed the univariate associations between exposure and the various bone-related variables and covariates (Table 2). A dwelling place located near or that functioned as an e-waste workshop was a risk factor that contributed to high BCLs. Good nutrition and eating habits such as consuming milk products and having a vitamin supplement were protective factors for the children. There was a significant positive correlation between BCLs and age. Having a dwelling place near or functioned as an e-waste workshop displayed a near-significant association (p=0.054) with BLLs. There was a strong positive correlation between blood lead and uDPD but not between osteocalcin and bALP. Similar effects were not seen for blood cadmium. In this analysis, serum total Ca levels showed a negative association with age, and also higher Ca levels were observed in girls compared to boys. We also found a negative association between uDPD and weight and height, and positive association between Ca levels and bALP and uDPD.

In a separate analysis of the covariates between subjects by cumulative Pb and Cd exposure status (i.e., low vs. high), we found that subjects with high cumulative Pb exposure

Table 1 Participant characteristics and data on exposure and bone-related variables among children in Guiyu

Characteristics	Mean	No.
Anthropometrics		
Age (years)	4.9±1.1	237
Weight (kg)	16.8±2.7	232
Height (cm)	101.3±8.0	231
BMI (kg/m²)	16.3±1.3	231
Biomarkers of exposure		
Blood Pb (μg/dL)	7.30 (4.33–15.43)	232
Blood Cd (μg//L)	0.69 (0.36–1.45)	231
Biomarkers of effect		
Serum total calcium (mmol/L)	2.39 (1.80–2.68)	190
Serum osteocalcin (ng/mL)	4.55 (2.09–12.55)	215
Serum bone alkaline phosphatase (U/L)	58.40 (37.56–91.76)	208
Urinary deoxypyridinoline (nmol/g creatinine)	34.87 (13.91–184.99)	146

Values are arithmetic mean±SD, median (5th–95th percentile interval)

Table 2 Spearman correlation coefficients between exposure and some investigated factors (Spearman rank correlation)

	BLLs	BCLs	Height	Weight	BMI	Calcium	Osteocalcin	bALP	u-DPD
Age	−0.021	0.310***	0.793***	0.652***	−0.239***	−0.338***	−0.094	−0.131*	−0.179**
Sex	−0.117*	0.107	0.034	−0.036	−0.139**	0.173**	0.055	0.025	0.013
BLL		0.127*	−0.119	−0.128	0.022	0.126*	0.020	0.087	0.239***
BCL	0.127*		0.252***	0.228***	−0.012	−0.029	0.009	−0.055	−0.024
Height	−0.119*	0.252***		0.862***	−0.220***	−0.274***	−0.094	−0.105	−0.204**
Weight	−0.128*	0.228***	0.862***		0.257***	−0.203***	−0.088	−0.067	−0.179**
BMI	0.022	−0.012	−0.220***	0.257***		0.136*	−0.001	0.071	0.044
Calcium	0.126*	−0.029	−0.274***	−0.203***	0.136*		0.124*	0.267***	0.208***
Osteocalcin	0.020	0.009	−0.094	−0.088	−0.001	0.124*		0.113	−0.005
bALP	0.087	−0.055	−0.105	−0.067	0.071	0.267***	0.113		0.162*
uDPD	0.239***	−0.024	−0.204**	−0.179**	0.044	0.208***	−0.005	0.162*	
Number of milk products that child had per month	−0.090	−0.025***	0.071	0.089	0.059	−0.026	−0.053	0.043	0.000
Number of vitamin products per child per month	−0.030	−0.229***	0.052	0.056	0.067	0.015	0.127	0.028	−0.005
Average monthly household income	0.009	−0.154*	0.087	0.104	0.023	−0.020	0.095	0.088	0.077
E-waste workshop around the house	0.144*	0.172**	0.039	0.023	−0.048	−0.014	−0.073	−0.074	0.104

* $0.05 < p < 0.1$; ** $p < 0.05$; *** $p < 0.01$

had a higher uDPD and serum calcium than the subjects with low cumulative Pb exposure (Table 3). We further evaluated the associations between exposure and physical growth variables by adjusting for age and sex (Table 4). This was done because age and gender were shown to be strongly associated with the physical growth of the children in a multiple linear regression analysis. In this adjusted model, BLLs showed a significant negative association with height and weight. However, the association between Cd and physical growth indexes (height, weight, and BMI) became insignificant. In an exploratory analysis, we studied the associations of biomarkers of exposure. BLLs were associated with increases in the urinary excretion of DPD. The serum total Ca increased with age (Table 5).

Table 3 Comparison of covariates by cumulative lead exposure status (low vs. high)

Covariates	Low [median= 5.91 (3.30–7.30)] μg/dL	High [median= 9.12 (7.31–24.90)] μg/dL	p value
Anthropometrics			
Sex (% male)	52.20	61.7	0.14[b]
Age (years)	5	5	0.91[c]
Weight (kg)	16.83	16.60	0.47[c]
Height (cm)	101.84	100.69	0.28[c]
BMI (kg/m²)	16.19	16.32	0.45[c]
Exposure biomarker			
Blood Cd (μg//L)	0.66	0.73	0.05[a]
Effects biomarker			
Calcium (mmol/L)	2.37	2.41	0.04[a]
Osteocalcin (ng/mL)	4.65	4.51	0.87[a]
bALP (U/L)	53.39	62.05	0.39[a]
uDPD (nmol/g)	32.51	42.27	0.03[a]

Values are arithmetic mean or median

[a] By Mann–Whitney U statistic

[b] By chi-square test

[c] By t test

Table 4 Multiple linear regression analysis of physical growth index as a function of age, sex, blood cadmium, and blood lead

Dependent variable	Independent variable	β	p value
Model 1	R^2	0.62	
Height	Age	0.79	0.00
	Blood lead levels	−0.10	0.02
	Blood cadmium levels	−0.02	0.59
	Sex	0.02	0.66
Model 2	R^2	0.43	
Body weight	Age	0.65	0.00
	Blood lead levels	−0.14	0.01
	Blood cadmium levels	0.00	0.98
	Sex	−0.05	0.38
Model 3	R^2	0.06	
BMI	Age	−0.23	0.00
	Blood lead levels	−0.08	0.24
	Blood cadmium levels	0.05	0.45
	Sex	−0.15	0.03

R^2 explained adjusted variance for the total model

Table 5 Independent associations of effect biomarkers with lead and cadmium exposure as reflected by BLLs and BCLs

	Calcium (mmol/L)	Calcitonin (ng/mL)	bALP (U/L)	uDPD (nmol/g)
R^2	0.18	0.08	0.06	0.18
Partial regression coefficients((±SE)				
Blood lead levels	NS	NS	NS	10.09±3.76***
Blood cadmium levels	0.04±0.02*	NS	NS	NS
Age	−0.04±0.01***	−0.48±0.26*	−2.28±1.35*	NS
Sex	NS	NS	NS	NS
Body mass index	0.02±0.01*	NS	NS	NS
Cigarette consumption by father everyday	NS	NS	NS	17.30±10.28*
Average monthly household income	NS	NS	NS	NS
Use of supplement of calcium/vitamin D	NS	0.77±0.38*	NS	NS

NS not significant

*$0.05 < p < 0.1$; **$p \leq 0.05$; ***$p \leq 0.01$, significance of the partial regression coefficients

Discussion

In this study, a higher BLL was associated with reduced height and increased bone resorption in children living in Guiyu which is consistent with our primary hypothesis. There was no association between Cd exposure and bone metabolism. However, this was the first comprehensive assessment of the association linking Pb and Cd exposure to childhood bone growth and bone and Ca metabolism following adjustment for age and sex.

It is difficult to find a perfect dose estimate for either Pb or Cd due to the prevalence of so many other toxic agents. Blood Pb is the most frequently used dose estimate for Pb and is a commonly used indicator of the total body burden by WHO (1995). The half-life of Pb in blood is short, about 36 days, which typically represents recent exposure. Methods for detecting low Pb levels in bone with in vivo X-ray fluorescence are now available (Hu et al. 1998) but are not easily accessible. The dose estimate most often used for Cd is urinary Cd. Blood Cd is considered the most valid marker for recent exposure. However, accumulated Cd in the body will influence the blood Cd concentrations. Therefore, even after exposure ceases the concentration in blood will not decrease to the pre-exposure levels. As a result, Cd in blood may serve as a good estimate of the overall accumulated body burden. The reported correlation coefficient between Cd in blood and urine was 0.6 (Järup and Kesson 2009).

Pb is considered to be one of the major heavy metal contaminants during the process of e-waste recycling (Wong et al. 2007). We found that having a dwelling place near or functioning as an e-waste workshop contributed to high BLLs in children. In this study, the mean child BLL was 7.30 μg/dL, much lower in comparison to our previous studies conducted in Guiyu (Huo et al. 2007; Zheng et al. 2008). However, local children are still under great risk considering the fact that source of the environmental contaminants still exists and no safe threshold for BLLs in young children has been identified by the Centers for Disease Control and Prevention (2005).

Childhood Pb exposure has been attributed to adult disorders such as osteoporosis (Goyer et al. 1994; Gruber et al. 1997; Nash et al. 2004). An alternative model for the development of osteoporosis is that Pb-exposed individuals may achieve a lower peak bone mass as a young adult. This study supports prior studies showing a negative association between BLLs and height in children (Frisancho and Ryan 1991; Kim et al. 1995; Min et al. 2008; Shen et al. 2001) Similarly, Zuscik et al. found that Pb has an effect on the growth plate by the induction of chondrogenes and by reducing chondrocyte maturation, resulting in delayed endochondral bone formation and suggested that the possible mechanism for this process was through the modulation and integration of multiple signaling pathways including TGF-β, BMP, AP-1, and NFκB (Zuscik et al. 2007, 2002). Animal experiments demonstrated that Pb exposure can inhibit fracture healing in mice, with complex effects noted on chondrogenesis and chondrocyte maturation (Carmouche et al. 2005).

Another potential mechanism is that lead affects bone at a cellular level and induces bone loss. Reports have shown that Pb may exert both direct and indirect actions on bone turnover; indirectly through changes in the circulating levels of hormones, particularly 1,25-dihydroxyvitamin D3, which modulate bone cell function, and directly on osteoblast and osteoclast function (Berglund et al. 2000; Pounds et al. 1991). In line with these experimental studies, we found there is an association between BLL and bone resorption. We suggest that lead affects bone resorption (osteoclasts), resulting in increased uDPD and serum calcium levels. Such stimulation of bone resorption has been demonstrated in both animal and in vitro studies (Escribano et al. 1997; Gruber et al. 1997). It has been observed in bone cultures that Pb increases bone resorption by a mechanism involving PGE2 which increases the intracellular levels of cAMP and calcium ions (Miyahara et al. 1995).

In this investigation, no association between bone formation biomarkers and Pb exposure was found. The possible explanation is that Pb exposure at this level was not significant

enough to have that effect. In our study, the mean BLL for the local children was 7.30 μg/dl (range, 3.30–24.90). Epidemiological studies have shown that children with increased Pb absorption have a reduction in 1α, $25 (OH)_2 D_3$ concentration which returned to normal once blood Pb decreased to <30 μg/dl (1.4 μmol/l; Rosen et al. 1980).

Despite the extensive research on the effects of Pb on bone metabolism, population studies are limited. In children, high blood Pb was associated with higher BMD (Campbell et al. 2004). Contrary to this, another study found no correlation between blood Pb and BMD (Alfvén et al. 2002). We also found no association between blood Cd and bone turnover biomarkers. Two recent studies also reported no convincing association between low blood Cd exposure and bone (Rignell-Hydbom et al. 2009; Trzcinka-Ochocka et al. 2010). Cd accumulates with age, thus elderly women constitute a high risk group (Järup and Kesson 2009). This study showed that the children may be too young to have bone problems resulting from low cadmium exposure.

Conclusion

In this population study, no association between Cd exposure and bone metabolism biomarkers was found. However, considering Cd accumulates with age, childhood exposure might pose a risk for these children later in life. An adverse effect of Pb exposure on bone growth was demonstrated in this study. An exposure-dependent relationship was found between BLL and bone resorption biomarkers. Childhood Pb exposure may cause adult osteoporosis. Limitations of our study include the cross-sectional design and the difficulty in adjusting for potential confounders. Many other pollutants, such as POPs, also exist in this environment and in the human body, and have the potential to act as confounding factors. A prospective study would be required to confirm this causal finding.

Conflict of interest The authors declare that there are no conflicts of interest.

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