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Decreased lung function with mediation of blood parameters linked to e-waste lead and cadmium exposure in preschool children☆

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ABSTRACT

Blood lead (Pb) and cadmium (Cd) levels have been associated with lower lung function in adults and smokers, but whether this also holds for children from electronic waste (e-waste) recycling areas is still unknown. To investigate the contribution of blood heavy metals and lung function levels, and the relationship among living area, the blood parameter levels, and the lung function levels, a total of 206 preschool children from Guiyu (exposed area), and Haojiang and Xiashan (reference areas) were recruited and required to undergo blood tests and lung function tests during the study period. Preschool children living in e-waste exposed areas were found to have a 1.37 μg/dL increase in blood Pb, 1.18 μg/L increase in blood Cd, and a 41.00 × 10^9/L increase in platelet counts, while having a 2.82 g/L decrease in hemoglobin, 92 mL decrease in FVC and 86 mL decrease in FEV_1. Each unit of hemoglobin (1 g/L) decline was associated with 5 mL decrease in FVC and 4 mL decrease in FEV_1. We conclude that children living in e-waste exposed area have higher levels of blood Pb, Cd and platelets, and lower levels of hemoglobin and lung function. Hemoglobin can be a good predictor for lung function levels.

1. Introduction

Electronic waste (e-waste) is defined as any discarded, obsolete, or broken electrical or electronic devices or products nearing the end of their useful life, which has become the largest growing amount of waste in the world (Zhang et al., 2012; Grant et al., 2013; Zeng et al., 2016a,b,c). It was estimated that global e-waste generation was 41.8 million tonnes in 2014 and increases at the rate of about 11% annually (Breivik et al., 2014; Heacock et al., 2016; Wang et al., 2016a,b). Approximately 70% of e-waste is illegally exported or dumped by developed countries to China (Zhang et al., 2012; Awasthi et al., 2016; Wang et al., 2016a,b). E-waste cannot be regarded or treated like any other type of waste because it contains blends of hazardous metals (60%), plastics (30%), and other materials (10%) (Widmer et al., 2005; Wong et al., 2007a,b; Chen et al., 2009; Wittsiepe et al., 2015; Wang et al., 2016a,b). Heavy metals can not only be degraded into less hazardous end products, but can also be taken up by environmental media such as air, dust, soil, water, and sediment (Wong et al., 2007a,b; Guo et al., 2009; Song and Li, 2014), and accumulate in the human body through inhalation, ingestion, and dermal absorption (Song and Li, 2015; Zeng et al., 2016a,b,c; Zhang et al., 2016). Heavy metals such as lead (Pb) and cadmium (Cd) mainly enter the human body through respiration and concentrate in tissues and organs via the blood circulation. They are deposited in the bronchioles and alveoli of the airways in the form of aerosols, dust and steam. Heavy metal exposure may contribute to increased oxidative stress, disruption of barrier mechanisms, inflammation and tissue destruction in the lungs (Kirschvink et al., 2006). Only a few studies have demonstrated that blood Pb and blood Cd levels were associated with lower lung function levels in adults. Whether this also holds for

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children (who are more susceptible) from e-waste recycling areas was not explored and therefore still unclear (Pak et al., 2012; Park and Lee, 2013; Oh et al., 2014).

With a 30-year history of e-waste disposal and recycling with little or no regulation, Guiyu has become one of the largest e-waste destinations and recycling areas in China and worldwide. About 70% of the e-waste imported or generated by China was processed in Guiyu (Wu et al., 2010; Chen et al., 2011), which leads to its highest level of e-waste pollution in the world (Huo et al., 2007; Ogunseitan et al., 2009; Wang et al., 2016a,b). Informal e-waste recycling and disposing process not only contributes to serious pollution but also threat to human health. Previous studies reported high levels of Pb and Cd concentrations in Guiyu compared to many other areas in $PM_{2.5}$ (Deng and Wong, 2006; Zeng et al., 2016b,c), dust (Leung et al., 2008; Yekeen et al., 2016), soil (Fu et al., 2008; Yekeen et al., 2016), water (Wong et al., 2007; Guo et al., 2009), and sediment (Wong et al., 2007a,b; Guo et al., 2009). Several cross-sectional studies demonstrated high levels of blood Pb and Cd were presented in Guiyu for years (Huo et al., 2007; Zheng et al., 2013; Zeng et al., 2016a,b,c; Lin et al., 2017). Strak et al. showed a significant associations between lung function levels of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) with trace metals such as Fe, Cu, and Ni in $PM_{2.5}$ and PM_{10} (Strak et al., 2012). Nearly 76% of e-waste workers suffered from respiratory symptoms or diseases including dyspnea, cough, bronchitis, and asthma according to a survey conducted by the Associated Chambers of Commerce and Industry of India (Sharma, 2015). Recently, our study found that the levels of Pb and Cd both in $PM_{2.5}$ and in blood, as well as the prevalence of respiratory symptoms cough, dyspnea, phlegm and wheeze in preschool children (3-to-8-years of age) were higher in Guiyu compared to the reference areas (Zeng et al., 2016c). In addition, one of our previous studies demonstrated that there was no difference in FVC of primary school children aged 8–13 years old between the exposed and reference area (Zheng et al., 2013). However, FVC was significantly lower in Guiyu children compared to those from the reference area in the youngest age group (8–9 years). It seems like that younger children are the particular more sensitive and vulnerable population compared to older children and adults.

In view of the lack of reports concerning the association between blood heavy metal and lung function levels in younger preschool children from e-waste recycling areas, we recruited 206 preschool children aged 5–7 years from Guiyu (the exposed area), and Haojiang and Xiashan (the reference areas). We measured the blood parameter levels such as Pb, Cd, hemoglobin, platelet counts and performed spirometry to obtain FVC and FEV_1 lung function levels. This study aims to determine blood parameters such as blood Pb, Cd, hemoglobin and platelets, evaluate their effect on lung function levels, and offer a deeper understanding of the effect of living in e-waste exposed area on lung function levels.

2. Materials and methods

2.1. Study areas and population

The sampling site was located in Guiyu town (exposed area), Shantou city, in the southeastern coast of Guangdong province in China. Haojiang (the first reference area) is located 31.6 km to the east of Guiyu and Xiashan (the second reference area) is located 5.8 km to the southeast of Guiyu (Fig. 1) (Huo et al., 2007). There are similar demographic characteristics, life-styles, eating habits, and traffic conditions in these three areas. Haojiang and Xiashan were selected as the reference areas because they lack e-waste pollution. A total of 206 preschool children, 5-to-7-years old, were recruited from three kindergartens from Guiyu ($n = 100$), Xiashan ($n = 54$), and Haojiang ($n = 52$) during the period of November 2013 and December 2013. Participant received a general health questionnaire. All parents or guardians of the participants gave their written informed consent after receiving detailed explanations of the study and potential consequences prior to enrollment. This study protocol was approved by the Human Ethical Committee of Shantou University Medical College, China.

2.2. Physical growth and development test

Physical growth and developmental parameters such as body height, body weight, and chest circumferences were measured at the time of blood sample collection. Height and weight were measured using a weight and height scale (TZ120; Yuyao Balance Instrument Factory, Yuyao, China). Children were required to remove their shoes, take off their coat, and maintain a certain standing posture prior to being measured. All measurements were carried out by a trained physician (Liu et al., 2011).

2.3. Spirometry

Spirometry was conducted with a portable spirometer (Jiangsu Jintan Medical Instrument Factory, Model DF-II, Jintan, China), using standardized procedures following ATS-criteria (Miller et al., 2005). Participants practiced the use of the mouthpiece with the spirometer until they felt comfortable under the guidance of the field physician. Results of three readings were recorded, and the highest reading of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) was used in the analysis.

2.4. Questionnaire

We collected information on potential routes of exposure to e-waste, lead and cadmium, as well as general demographic and health parameters with a general questionnaire (Zeng et al., 2016c). The basic information collected by the questionnaire included age; gender; birth weight; family member daily smoking; socioeconomic status such as parental education levels and family income levels; eating habits such as eating daily products, eating preserved eggs, and eating canned food; behavior habits such as biting fingers or nails, biting pencils or erasers, biting toys, washing hands before eating, contact with e-waste, and outdoor daily play time; home location information such as distance from home to a road, and home close to e-waste within 50 m; and other factors such as ventilation of house, closed windows, and home used as workplace. The parents or guardians of the children recruited in this study completed the questionnaire.

2.5. Blood sample analyses

Venipuncture was performed by nurses, and blood was collected and stored in metal-free tubes at minus 20 °C until analysis. Hemoglobin, hematocrit, platelet counts, thrombocytocrit, and red blood cell distribution width (RDW) were measured using an automatic hematology analyzer (Sysmex XT-1800i). RDW was considered a biomarker for nutritional status because an increased RDW is associated with nutritional deficiency (Grant et al., 2013). Blood Pb and blood Cd determinations were performed by graphite furnace atomic absorption spectrophotometry (Jena Zenit 650). The detailed procedure for measuring blood Pb and blood Cd was previously described in our previous studies (Guo et al., 2010; Zeng et al., 2016c). Briefly, 100 μL blood and 900 μL of 0.5% nitric acid for BPb, or 200 μL blood and 800 μL of 5% nitric acid for BCd were placed into tubes. The mixture was immediately shaken and then allowed to digest for 10 min. Unlike BPb measurements, after

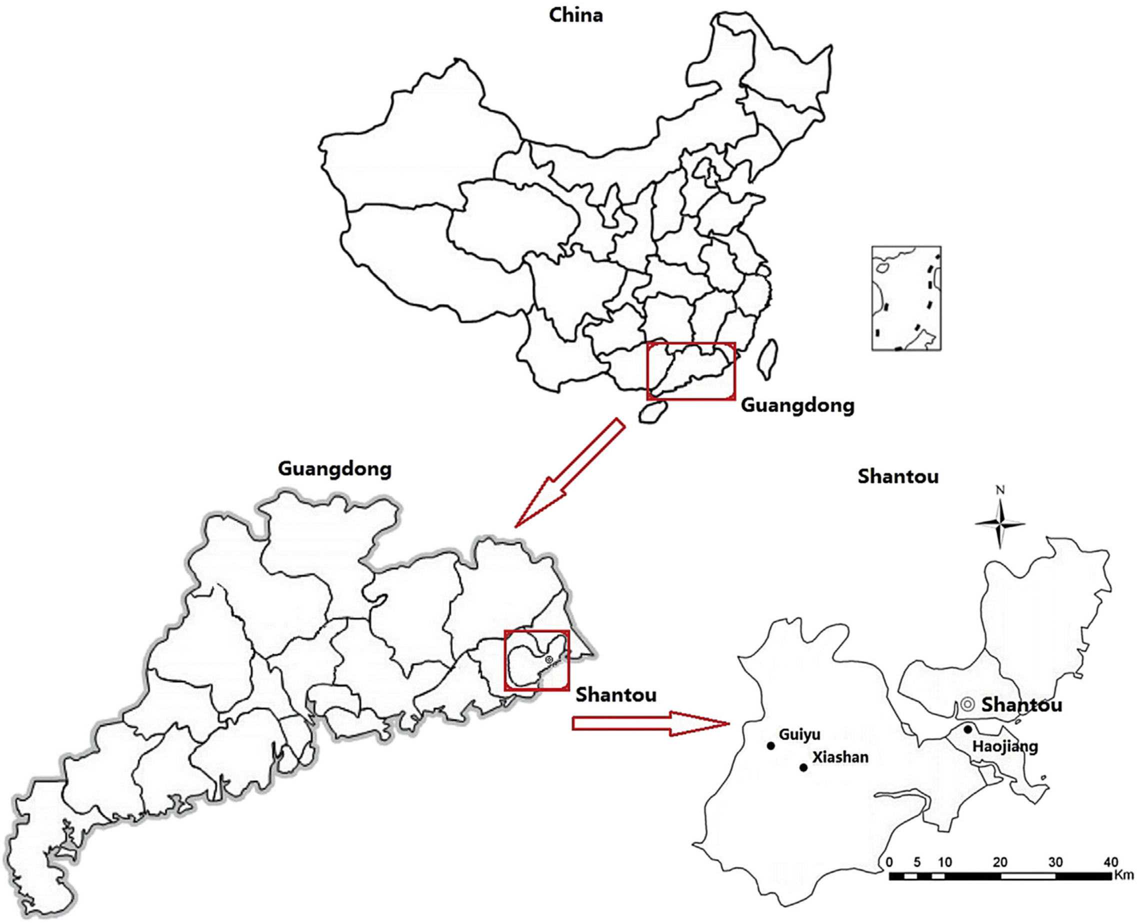

Fig. 1. The location of the sampling sites (Guiyu, Haojiang and Xiashan).

digestion BCd solutions were centrifuged for 15 min at 3000 r.p.m. to separate the supernatant. During instrumental analysis, a calibration curve was performed every 10 samples to verify the stability of the instrument calibration. Precision for BPb and BCd was expressed as the relative standard deviation (RSD) which was required to be less than 15%. Linearity for a five-point heavy metal calibration curve was good for both BPb and BCd ($r^2 > 0.995$). The spiked recovery of BPb and BCd were generally within the 94–107%.

2.6. Statistical methods

Data was expressed as median and interquartile range, or mean and standard deviation as appropriate according to its characteristics. The independent samples *t*-test was used to test group differences of normally distributed data. The chi-square test was used to test group differences of non-normally distributed data. Confounders such as age and gender, and age, gender and height were included in the basic linear regression models when investigating the blood parameters and lung funciton levels, respectively. In addition, the association between living area (the exposed vs. reference areas) and the blood parameter levels and lung function levels were analyzed by several linear regression models adjusted for the possible confounders. Family members daily smoking, socioeconomic status, eating habits, behavior habits, nutrition and other potential confounders were included in the each final model when the p-value of the confounder was lower than 0.05. Furthermore, several linear regression models were performed with and without the blood parameters to investigate whether the blood parameters mediate the association between living area and lung function levels. Blood parameters were regarded as mediators when they changed the estimate for living area on lung function by more than 10% compared to the final models or when the p-value of the confounder was lower than 0.05. Finally, the association between blood parameters and lung function levels was assessed using multiple linear regression models. P-values < 0.05 were considered statistically significant. All analyses were performed in SPSS version 22.0 (IBM Corporation, NJ, USA).

3. Results

3.1. General characteristics of the study population

A total of 206 preschool children were recruited in the study (Table 1). The mean age of preschool children in the exposed area ($n = 100$) was 5.53 ± 0.51 years, and 5.54 ± 0.56 in the reference areas ($p > 0.05$). Gender, weight and body mass index (BMI) of children did not show significant differences (all $p > 0.05$). Birth weight and current height of children was lower in the exposed area compared to those in the reference areas ($p < 0.05$). Parents of children from the exposed area had a lower education, family income, while had a higher smoking prevalence ($p < 0.05$). The blood parameter information is shown in Table 2. The mean blood Pb level in the exposed group was higher compared to the reference areas (5.53 (3.92–7.04) μg/dL vs. 3.57 (2.68–4.86)) μg/dL) (Table 2, $p < 0.05$). No significant difference was found in blood Cd level in

Table 1
Demographic characteristics of the study population.

Characteristics	Exposed area (n = 100)	Reference areas (n = 106)	P-value
Age (years)	5.53 ± 0.51	5.54 ± 0.56	0.881[a]
Gender, n (%)			0.283[b]
boys	52 (52.0)	63 (59.4)	
girls	48 (48.0)	43 (40.6)	
Birth weight (kg)	3.07 ± 0.49	3.25 ± 0.58	0.020[a]
Height (cm)	111.03 ± 5.95	112.56 ± 4.70	0.045[a]
Weight (kg)	19.30 ± 2.84	19.76 ± 2.46	0.412[a]
Body mass index (BMI, kg/m^2)	15.43 (14.86–16.33)	15.12 (14.35–16.24)	0.128[c]
Family member daily smoking, n (%)			<0.001[b]
non-smoking	31 (31.0)	58 (54.6)	
< 2 cigarettes	14 (14.0)	11 (10.4)	
2–10 cigarettes	23 (23.0)	16 (15.1)	
11–20 cigarettes	26 (26.0)	14 (13.3)	
> 20 cigarettes	6 (6.0)	7 (6.6)	
Parental education level, n (%)			<0.001[b]
illiteracy	6 (6.0)	2 (1.9)	
primary school	4 (4.0)	3 (2.8)	
middle school	52 (52.0)	20 (18.9)	
secondary school	25 (25.0)	22(20.7)	
high school	11 (11.0)	20 (18.9)	
college/university	2 (2.0)	39 (36.8)	
Family income level per month (¥), n (%)			0.001[b]
< 1500	18 (18.0)	6 (5.7)	
1500 - 3000	24 (24.0)	14 (13.2)	
3000 - 4500	18 (18.0)	19 (17.9)	
4500 - 6000	18 (18.0)	18 (17.0)	
> 6000	22 (22.0)	49 (46.2)	
Distance between home and road (m), n (%)			<0.001[b]
< 10	44 (44.0)	16 (15.1)	
10 - 50	21 (21.0)	23 (21.7)	
50 - 100	14 (14.0)	34 (32.1)	
> 100	21 (21.0)	33 (31.1)	
Parents engaged in e-waste recycling, n (%)			<0.001[b]
no	61 (61.0)	99 (93.4)	
yes	39 (39.0)	7 (6.6)	
Home close to e-waste within 50 m, n (%)			<0.001[b]
no	53 (53.0)	101 (95.3)	
yes	47 (47.0)	5 (4.7)	
Children contact with e-waste, n (%)			<0.001[b]
no	68 (68.0)	105 (99.1)	
yes	32 (32.0)	1 (0.9)	

Exposed area: Guiyu; Reference areas: Haojiang and Xiashan.
[a] Analysis by independent-sample *t*-test.
[b] Analysis by chi-square test.
[c] Analysis by Manne-Whitney *U* test. For continuous variables, average range is presented as mean values ± SD (normal distribution data) or median values with inter-quartile (non-normal distribution data).

children between the exposed and reference areas ($p > 0.05$). The blood hemoglobin and hematocrit levels were lower in the exposed area compared to the reference areas. While the blood platelet and thrombocytosis level were higher in the exposed group than those in the reference groups (Table 2). Children from the exposed area have higher FVC and FEV_1 lung function levels compared to the reference areas ($p < 0.05$). However, no significant difference was found in the ratio of FVC to FEV_1 between the exposed group and the reference areas. Other information obtained from the questionnaire such as behavior habits, eating habits, and home location information are shown in Table 1 and Table S1.

3.2. Blood parameter levels and related factors

BPb of preschool children from non-smoking family were lower in Guiyu than those in the reference areas, but BCd of preschool children showed no significant difference between Guiyu and the reference areas (Table S5). In further linear regression analyses, family member smoking was not associated with BPb and BCd levels of preschool children (Table S6). Multiple linear regression analysis was used to estimate and identify the specific factors that were associated with the blood parameter levels of Pb (Table 3), Cd (Table 3), hemoglobin (Table S3), and platelets (Table S3). We found that variable about children living in the exposed area, children in contact with e-waste, parents engaged in e-waste recycling, home within 50 m of e-wastearea, biting pencils or erasers, eating canned foods were all positively associated with blood Pb levels ($\beta = 0.420$, $\beta = 0.299$, $\beta = 0.295$, $\beta = 0.241$, $\beta = 0.207$, $\beta = 0.255$, respectively). Parental education level, family income levels, long distance between home and road, washing hands before eating were all negatively associated with blood Pb levels ($\beta = -0.328$, $\beta = -0.184$, $\beta = -0.157$, $\beta = -0.196$, respectively). In addition, hemoglobin, hematocrit and eating preserved eggs were positively associated with blood Cd levels ($\beta = 0.210$, $\beta = 0.190$, $\beta = 0.142$, respectively), whereas parental education level, family income levels, long distance between home and road, and eating dairy products all were negatively associated with blood Cd levels ($\beta = -0.305$, $\beta = -0.149$, $\beta = -0.149$, $\beta = -0.158$, respectively). Moreover, we found that long distance between home and road, and biting fingers or nails were positively associated with blood hemoglobin levels ($\beta = 0.176$,

Table 2
Levels of physical parameters, blood parameters, and lung function parameters in preschool children from Guiyu, Haojiang and Xiashan.

Characteristics	Exposed area (n = 100)	Reference areas (n = 106)	P-value
Blood parameters			
Pb (μg/dL)	5.53 (3.92–7.04)	3.57 (2.68–4.86)	<0.001[a]
Pb > 5 μg/dL, n (%)	58 (58.0)	26 (24.5)	<0.001[b]
Cd (μg/L)	0.58 (0.44–0.79)	0.57 (0.42–0.78)	0.717[a]
Red blood cell count, n (10^{12}/L)	4.84 ± 0.35	4.91 ± 0.39	0.162[c]
White blood cell count, n (10^9/L)	8.42 ± 2.25	8.27 ± 2.00	0.620[c]
Hemoglobin (g/L)	128.17 ± 8.28	131.49 ± 10.02	0.013[c]
Hematocrit (%)	39.27 ± 2.33	39.99 ± 2.73	0.048[c]
Platelet count (10^9/L)	338.03 ± 82.11	278.40 ± 77.86	<0.001[c]
Thrombocytocrit (%)	0.33 (0.29–0.38)	0.28 (0.24–0.32)	<0.001[d]
Thrombocytosis, n (%)	20 (20.0)	5 (4.7)	0.001[b]
RDW-SD (fL)	36.75 (35.70–38.20)	36.10 (34.70–37.48)	<0.001[d]
RDW-CV (%)	12.79 (12.40–13.10)	12.40 (12.10–12.80)	0.002[b]
Lung function parameters			
FVC (L)	1.23 ± 0.24	1.33 ± 0.25	0.004[c]
FEV_1 (L)	1.16 ± 0.21	1.24 ± 0.23	0.005[c]
FEV_1/FVC (%)	0.95 (0.91–0.97)	0.96 (0.92–0.98)	0.206[b]

Exposed area: Guiyu; Reference areas: Haojiang and Xiashan.
[a] Analysis by independent-sample *t*-test based on Ln-transformation.
[b] Analysis by chi-square test.
[c] Analysis by independent-sample *t*-test.
[d] Analysis by Manne-Whitney *U* test; FVC: forced vital capacity; FEV_1:forced expiratory volume in 1 s; FEV_1/FVC: the ratio of forced expiratory volume in 1 s to forced vital capacity; Pb: lead; Cd: cadmium. Thrombocytosis: platelet count >400 × 10^9/L. RDW: red blood cell distribution width. For continuous variables, average range is presented as mean values ± SD (normal distribution data) or median values with interquartile (non-normal distribution data).

Table 3
Multiple linear regression analysis of factors related to blood Pb levels and blood Cd levels in children.

	lnBPb			lnBCd		
	B[a]	β[b]	95% CI for B	B[a]	β[b]	95% CI for B
Living area	0.405	0.420	(0.278, 0.532)***	0.008	0.009	(-0.122, 0.137)
Hemoglobin (g/L)	−0.003	−0.004	(-0.010, 0.005)	0.010	0.210	(0.003, 0.017)**
Hematocrit (%)	−0.012	−0.063	(-0.039, 0.015)	0.033	0.190	(0.008, 0.058)**
Children contact with e-waste	0.390	0.299	(0.209, 0.570)***	−0.036	−0.030	(-0.208, 0.136)
Parents engaged in e-waste recycling	0.361	0.295	(0.192, 0.530)***	0.081	0.072	(-0.082, 0.245)
Home close to e-waste within 50 m	0.277	0.241	(0.119, 0.436)**	−0.004	−0.003	(-0.156, 0.149)
Parental education level	−0.128	−0.328	(-0.183, −0.074)***	−0.110	−0.305	(-0.160, −0.059)***
Family income level per month (¥)	−0.070	−0.184	(-0.124, −0.016)*	−0.052	−0.149	(-0.102, −0.002)*
Distance between home and road (m)	−0.067	−0.157	(-0.126, −0.007)*	−0.058	−0.149	(-0.113, −0.002)*
Washing hands before eating	−0.122	−0.196	(-0.211, −0.033)**	0.020	0.034	(-0.065, 0.105)
Biting pencils or erasers	0.268	0.207	(0.086, 0.450)**	0.051	0.042	(-0.123, 0.225)
Eating preserved eggs	−0.037	−0.047	(-0.146, 0.073)	0.104	0.142	(0.002, 0.207)*
Eating canned foods	0.223	0.255	(0.099, 0.347)***	−0.046	−0.057	(-0.164, 0.073)
Eating dairy products	−0.079	−0.122	(-0.170, 0.011)#	−0.096	−0.158	(-0.180, −0.011)*

Data was adjusted by age, gender, family member daily smoking; CI: confidence interval; B[a]: unstandardized coefficients; β[b]: standardized coefficients; Living area: Guiyu vs. Haojiang and Xiashan; *: p < 0.05; **: p < 0.01; ***: p < 0.001.

β = 0.159, respectively), while living in the exposed area and ventilation of house was negatively associated with blood hemoglobin levels (β = −0.184, β = −0.192, respectively). Furthermore, living in the exposed area and home close to e-waste within 50 were positively associated with blood platelet counts (β = 0.333, β = 0.175, respectively), but long distance between home and road and eating dairy products were negatively associated with blood platelet counts (β = −0.183, β = −0.157, respectively).

3.3. Lung function levels and related factors

Height was positively associated with FVC and FEV_1 according to the results of univariate linear regression analysis (data not shown). FVC and FEV_1 of boys were higher than girls no matter which areas they came from (Table S4). In addition, FVC and FEV_1 of boys were lower in Guiyu than in reference areas. However, FVC and FEV_1 of girls demonstrated no significant difference between Guiyu and the reference areas (Table S4). Moreover, FVC and FEV_1 of boys in Guiyu were lower than their predicted lung function levels, but FVC and FEV_1 of boys in the reference areas showed no siginicant difference when compared to their paired predicted lung function levels (Table S4). FVC of boys in Guiyu displayed no difference with their predicted values, while FVC of girls in the reference areas were lower than their predicted values. FEV_1 of boys and girls from Guiyu and the reference areas were lower than their predicted FEV_1, respectively (Table S4). Both FVC and FEV_1 of preschool children from non-smoking family were lower in Guiyu than those in the reference areas. However, both FVC and FEV_1 of preschool children from smoking family showed no sigificant difference between Guiyu and the reference areas (Table S5). Further analyses found that smoking was negatively associated with FVC and FEV_1 of preschool children (Table S6).

Multiple linear regression analysis was used to further estimate and identify the specific factors associated with lung function levels (Table 4). We found that living in the exposed area and closed windows were negatively associated with FVC (β = −0.129, β = −0.138, respectively), while hemoglobin and hematocrit were positively associated with FVC (β = 0.151, β = 0.170, respectively).

Living in the exposed area, long outdoor play time, and family member smoking were negatively associated with FEV_1 ($\beta = -0.134$, $\beta = -0.140$, $\beta = -0.151$, respectively), whereas hemoglobin and hematocrit were positively associated with FVC ($\beta = 0.135$, $\beta = 0.157$, respectively).

3.4. Associations between living area and the blood parameter levels

The relationship between living area and the levels of blood parameters including blood Pb, Cd, hemoglobin, and platelet counts are shown in Table 5. After adjusted for their respective confounding factors in the full multiple linear regression model, we found that living in Guiyu was positively associated with blood Pb levels ($\beta = 0.330$, $p < 0.001$), blood Cd levels ($\beta = 0.186$, $p < 0.05$) and blood platelet counts ($\beta = 0.226$, $p < 0.01$), and negatively associated with blood hemoglobin levels ($\beta = -0.128$, $p < 0.05$).

3.5. Associations between living area and the lung function levels

The association between living area and FVC and FEV_1 lung function levels are shown in Table 6. We found that living in Guiyu was associated with lower lung function levels both in the univariate model (FVC: $\beta = -0.198$, $p < 0.01$; FEV_1: $\beta = -0.194$, $p < 0.01$), the basic models (FVC: $\beta = -0.114$, $p < 0.05$; FEV_1: $\beta = -0.115$, $p < 0.05$) and the full multivariate linear regression models (FVC: $\beta = -0.186$, $p < 0.05$; FEV_1: $\beta = -0.192$, $p < 0.05$) (Table 6). Blood Pb, Cd, hemoglobin and platelet counts were included in the full model to assess whether these blood parameters mediated the association between living area and lung function levels. Blood Pb, hemoglobin and platelet counts changed the estimate for living area on lung function levels by more than 10% compared to the full model (p value of hemoglobin is less than 0.05), respectively, which indicated that blood parameters such as blood Pb, hemoglobin and platelet mediated the associations between living area and lung function levels (Table 6).

3.6. Associations between blood parameter levels and lung function levels

Spearman correlation analyses and multiple linear regression analyses were performed to assess the association between lung function levels and blood parameters including blood Pb, Cd, hemoglobin, and platelet counts (Table 7 and Table S2). We found that the blood hemoglobin levels were positively associated with FVC and FEV_1 both in the univariate model (FVC: $\beta = 0.154$, $p < 0.05$; FEV_1: $\beta = 0.135$, $p < 0.05$), basic models (FVC: $\beta = 0.156$, $p < 0.05$; FEV_1: $\beta = 0.141$, $p < 0.05$) and in the full models (FVC: $\beta = 0.158$, $p < 0.05$; FEV_1: $\beta = 0.150$, $p < 0.05$) (Table 7). No significant association between blood Pb, Cd, platelets and FVC and FEV_1 lung function levels was found in the full linear regression models (Table 7).

4. Discussion

This study investigated the effects of e-waste on the blood parameters and lung function levels in preschool children in one e-waste-exposed and two reference areas in China. Our results show that children living in the exposed area have higher levels of blood Pb and platelet counts, while have lower levels of hemoglobin, hematocrit, and lung function (FVC and FEV_1) levels compared to the reference population. In addition, we identified the specific questions in the questionnaire associated with blood parameter levels (Pb, Cd, hemoglobin, and platelet counts) and lung function levels as well. Moreover, after adjustment for potential confounders such as passive smoking, socioeconomic status, and nutritional status, living in the exposed area was still a risk for higher levels of blood Pb, Cd, and platelet counts, and risk for lower levels of hemoglobin, FVC, and FEV_1. It was worth noting that the blood parameters including Pb, hemoglobin and platelets mediated the association between living area and lung function levels, and blood hemoglobin may be a predictor for lung function levels.

The average blood Pb levels in children from the e-waste exposed area were 5.53 μg/dL. This is higher compared to the reference areas (3.57 μg/dL) and the updated U.S. CDC guidelines for blood Pb levels (5 μg/dL) (Betts, 2012). The U.S. CDC guidelines for blood Pb levels have been reduced from 10 μg/dL to 5 μg/dL in 2012, indicating that no level of lead exposure appears to be 'safe'. Our results indicate that e-waste exposure contributes to high blood Pb levels (Table 3). Currently, the average concentration of blood Pb in children from Guiyu is lower compared to our previous cross-sectional studies in 2004 (15.30 μg/dL) (Huo et al., 2007), 2006 (13.17 μg/dL) (Zheng et al., 2008), 2009 (7.33 μg/dL) (Liu et al., 2014), 2011 (6.76 μg/dL) (Zheng et al., 2013), and 2012 (6.24 μg/dL) (Zeng et al., 2016c). This may due to new strict policies, such as the Management Regulation on the Recycling of Waste Electrical and Electronic Products, and Regulations of Guangdong Province on Environmental Protection, promulgated and enforced by the local and national government in the last decade (Zeng et al., 2013, Zeng et al., 2016c; Tang, 2016). However, still 58.0% of the children in Guiyu had a blood Pb > 5 μg/dL in the current study, which suggests that lead pollution in Guiyu is still a very serious problem (Betts, 2012).

Similar to blood Pb levels, the average concentration of blood Cd (0.58 μg/L) in children from Guiyu in this study was lower than blood Cd levels in 2006 (1.58 μg/L) (Zheng et al., 2008) and in 2009 (0.69 μg/L) (Liu et al., 2014). It was the first time that blood Cd levels showed no significant difference between the exposed area and the reference areas. This may be because blood Cd levels were stable over the past four years in children from the exposed area, and

Table 4
Multiple linear regression analysis of factors related to lung function levels in children.

	FVC			FEV_1		
	B^a	β^b	95% CI for B	B^a	β^b	95% CI for B
Living area	−0.064	−0.129	(-0.125, −0.002)*	−0.059	−0.134	(-0.116, −0.002)*
Hemoglobin (g/L)	0.004	0.151	(0.001, 0.007)*	0.003	0.135	(0.000, 0.006)*
Hematocrit (%)	0.016	0.170	(0.004, 0.028)**	0.014	0.157	(0.003, 0.025)*
Blood Pb level (μg/dL)	−0.042	−0.083	(-0.107, 0.023)	−0.049	−0.106	(-0.109, 0.011)#
Close windows	−0.067	−0.138	(-0.132, −0.002)*	−0.058	−0.132	(-0.117, 0.002)#
Daily outdoor play time	−0.027	−0.112	(-0.058, 0.005)#	−0.030	−0.140	(-0.059, −0.001)*
Family member daily smoking	−0.020	−0.108	(-0.043, 0.003)#	−0.025	−0.151	(-0.046, −0.004)*

Data was adjusted by age, gender and height. B^a: unstandardized coefficients; β^b: standardized coefficients. CI: confidence interval; Living area: Guiyu vs. Haojiang and Xiashan; #: 0.05 < p < 0.10; *: p < 0.05; **: p < 0.01.

Table 5
The association between living areas and blood parameters.

	lnBPb[a] B (95% CI), β	lnBCd[b] B (95% CI), β	Hemoglobin[c] B (95% CI), β	Platelet count[d] B (95% CI), β
Living area				
Univariate model	0.407 (0.286, 0.528)***, 0.422	0.027 (−0.094, 0.148), 0.031	−3.320 (−5.932, - 0.708)*, −0.178	59.637 (35.094, 84.180)***, 0.327
Full model	0.317 (0.167, 0.467)***, 0.330	0.166 (0.021, 0.311)*, 0.186	−2.817 (−5.573, −0.061)*, −0.128	40.997 (10.948, 71.045)**, 0.226

Abbreviations, lnBPb: ln-transformation of blood lead; lnBCd: ln-transformation of blood cadmium; CI: Confidence intervals; B: unstandardized coefficients; β: standardized coefficients; Living area: Guiyu vs. Haojiang and Xiashan. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$. All full models adjusted for age and gender, family member daily smoking, parental education level, family income level, distance between home and road.

[a] Full model additionally adjusted for washing hands before eating, biting pencils or erasers, eating canned food, and eating dairy products.

[b] Full model additionally adjusted for washing hands before eating, eating preserved eggs, and eating dairy products.

[c] Full model additionally adjusted for ventilation of house, biting fingers or nails, biting pencils or erasers, and eating dairy products.

[d] Full model additionally adjusted for home close to e-waste within 50 m, and eating dairy products.

Table 6
The association between living areas and lung function mediated by blood parameters.

	FVC			FEV_1		
	B[a]	β[b]	95% CI for B	B[a]	β[b]	95% CI for B
Living in the e-waste exposed area						
Univariate model	−0.098	−0.198	(-0.165, −0.031)**	−0.087	−0.194	(-0.147, −0.026)**
Basic model	−0.064	−0.114	(-0.125, −0.002)*	−0.059	−0.115	(-0.116, −0.002)*
Full model	−0.092	−0.186	(-0.166, −0.018)*	−0.086	−0.192	(-0.155, −0.018)*
Full model + lnBPb	−0.087	−0.176	(-0.166, −0.009)*	−0.077	−0.171	(-0.149, −0.005)*
Full model + lnBCd	−0.095	−0.191	(-0.171, −0.019)*	−0.089	−0.198	(-0.158, −0.020)*
Full model + Hemoglobin	−0.078	−0.157	(-0.155, −0.002)*	−0.075	−0.166	(-0.145, −0.005)*
Full model + Platelet count	−0.107	−0.216	(-0.185, −0.030)**	−0.103	−0.230	(-0.174, −0.033)**

Abbreviations, lnBPb: ln-transformation of blood lead; lnBCd: ln-transformation of blood cadmium; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; CI: Confidence intervals; B: unstandardized coefficients; β: standardized coefficients; Living area: Guiyu vs. Haojiang and Xiashan; Basic model: Adjusted for age, gender, height, and family member daily smoking; Full model: Adjusted for age, gender, height, RDW, family member daily smoking, parental education level, family income level, and daily outdoor play time.*: $p < 0.05$; **: $p < 0.01$.

Table 7
The association between blood parameters and lung function.

	FVC			FEV_1		
	B[a]	β[b]	95% CI for B	B[a]	β[b]	95% CI for B
lnBPb						
Univariate Model	−0.047	−0.091	(-0.117, 0.024)	−0.052	−0.113	(-0.116, 0.011)
Basic model	−0.014	−0.028	(-0.088, 0.059)	−0.022	−0.047	(-0.089, 0.045)
Full model	−0.015	−0.029	(-0.093, 0.063)	−0.029	−0.062	(-0.100, 0.043)
lnBCd						
Univariate Model	−0.041	−0.073	(-0.119, 0.036)	−0.031	−0.060	(-0.101, 0.039)
Basic model	−0.003	−0.003	(-0.074, 0.067)	−0.001	−0.005	(-0.065, 0.064)
Full model	−0.018	−0.033	(-0.095, 0.059)	−0.017	−0.035	(-0.088, 0.053)
lnBPb*lnBCd						
Univariate Model	−0.019	−0.060	(-0.063, 0.025)	−0.012	−0.042	(-0.052, 0.027)
Basic model	−0.126	−0.393	(-0.275, 0.024)#	−0.127	−0.444	(-0.263, 0.008)#
Full model	−0.122	−0.397	(-0.276, 0.032)#	−0.129	−0.462	(-0.269, 0.011)#
Hemoglobin						
Univariate Model	0.004	0.154	(0.000, 0.008)*	0.003	0.135	(0.000, 0.007)*
Basic model	0.004	0.156	(0.001, 0.008)*	0.003	0.141	(0.000, 0.007)*
Full model	0.005	0.158	(0.001, 0.008)*	0.004	0.150	(0.000, 0.007)*
Platelet count						
Univariate Model	0.088	0.032	(-0.298, 0.473)	0.169	0.069	(-0.178, 0.515)
Basic model	0.329	0.119	(-0.044, 0.703)#	0.393	0.159	(0.056, 0.731)*
Full model	0.290	0.107	(-0.097, 0.677)	0.343	0.139	(-0.009, 0.695)#

Abbreviations, FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; lnBPb: ln-transformation of blood lead; lnBCd: ln-transformation of blood cadmium; Platelet count unit: (109/L)/(1000); RDW: red blood cell distribution width; CI: Confidence intervals; B: unstandardized coefficients; β: standardized coefficients; Basic Models: Adjusted for age, gender, height, family member daily smoking, and living area; Full Model: Adjusted for age, gender, height, family member daily smoking, family income level, parental education level, daily outdoor play time, and living area. #: $0.05 < p < 0.10$; *: $p < 0.05$; **: $p < 0.01$.

increased blood Cd levels in the reference areas (i.e. Median of blood Cd from Haojiang was 0.50 μg/L in 2012, and 0.57 μg/L in 2013) (Zeng et al., 2016c). Noteworthy, this higher blood Cd levels in the reference areas may be due to dust exposure from fly ash pollution of a thermal power plant in Haojiang (one of the reference areas) (Zeng et al., 2016c). In addition, we found that eating preserved eggs was a risk factor for blood Cd levels, whereas high parental education levels, high family income levels, long distance between home and road, and eating dairy products were protective factors for blood Cd levels (Table 3). Even after adjusting for confounders, there is still a risk for higher blood Cd levels when living in e-waste exposed area (Table 5), which indicates that Cd accumulation from e-waste exposed area continuously affects local people, and in particular for children. Moreover, most children had blood Cd > 0.2 μg/L (the current suggested toxicity threshold of blood Cd) (Cao et al., 2009), which was still higher than the blood Cd of children from America (0.23 μg/L), Africa (0.21 μg/L), and Europe (0.15 μg/L) (Hruba et al., 2012). Therefore, it is necessary to continue to monitor cadmium exposure, especially in e-waste exposure areas.

It is known that both passive smoking, socioeconomic status (Hegewald and Crapo, 2007) and nutrition (Steinkamp and Wiedemann, 2002) are important potential confounders for lung function, which cannot be ignored when studying the possible factors of lung function levels. Lung function levels of preschool from non-smoking family may be greatly influenced by living area, while lung function levels of preschool from smoking family might be mainly affected by family member smoking status (Table S5). In short, family member smoking contribute to lung function levels of preschool children (Table S6). Compared to girls, lung function of boys are more susceptible to where they live (Table S4). In addition, lung function levels of preschool children both in Guiyu and in the reference areas were lower than their predicted value (Table S4). After adjusting for these confounders, we found that children living in the exposed area had reduced FVC (92 mL) and FEV_1 (86 mL) (Table 6). This is in agreement with our previous observation that younger children are particularly more sensitive and vulnerable to environmental pollution, and are more susceptible to lung function impairments compared to older children or adults for many reasons: yonger children are exposed to toxins via additional routes of exposure (breast feeding, placental transmission), have high-risk behaviors (hand to mouth and object to mouth exposure), are more active, have a larger ratio between respiratory capacity to body weight, a bigger surface area in relation to body weight, and lower clearance rate of toxins (Leith and Carpenter, 2012; Grant et al., 2013; Zeng et al., 2016b,c). In the current study, we demonstrated that blood Pb, hemoglobin, and platelets mediated the association between living area and lung function levels (Table 6). In addition, each unit of hemoglobin (1 g/L) decline was associated with 5 mL decrease in FVC and 4 mL decrease in FEV_1 in preschool children (Table 7). Therefore, blood hemoglobin levels may can be used as a predictor for lung function levels.

Heavy metals such as Pb and Cd can generate reactive oxygen species (ROS), which can trigger oxidative stress in the lungs (Stohs and Bagchi, 1995). ROS can cause damage to pulmonary capillary endothelial cells, alveolar epithelial cells and basilar membrane cells. It also leads to alveolar collapse, atelectasis and alveolar ventilation dysfunction (Bersten et al., 1998). Several studies demonstrated that heavy metals, such as Pb and Cd, were associated with lower lung function level in adults (Pak et al., 2012; Oh et al., 2014; Leem et al., 2015). Moreover, an inverse dose-response association was observed between urinary lead and FEV_1/FVC ratio in adults (Feng et al., 2015), and lead and manganese in atmospheric particulate matter (PM) were associated with a decreased peak expiratory flow rate of schoolchildren (Hong et al., 2007). However, the association between heavy metal exposure and lung function levels in children is still unclear. In the current study, we did not find a significant association between blood Pb and Cd, the joint effects of blood Pb and Cd, and lung function levels, respectively (Table 7). This may mainly be due to that previous studies were based on adult populations, such as occupational workers and smokers (Pak et al., 2012; Oh et al., 2014; Leem et al., 2015), and partly due to the vulnerability of children when compared to adults (Leith and Carpenter, 2012; Grant et al., 2013; Zeng et al., 2016b,c). Children are in the stage of rapid growth and lung development, and are therefore considered to be more susceptible to hazardous environmental pollutants compared to adults. In addition, the adverse effects of heavy metals on lung function may be delayed in childhood and manifested in an adult stage.

Heavy metals such as Pb and Cd can disturb the synthesis of hemoglobin through impaired heme synthesis, iron metabolism, and the production of erythropoietin (Chen et al., 2015). Associations between blood Pb, Cd and hemoglobin have been investigated by a few studies in adults, but the results are inconsistent and inconclusive (Rondo et al., 2006; Rabsteina et al., 2008; Kordas et al., 2011; Chen et al., 2015). In the current study, no association was found between blood Pb levels and hemoglobin in children, which may be due to complex toxicokinetics and co-exposure of heavy metals, and its nonlinear relationship with health effects (Barbosa et al., 2005). This study demonstrated that living in e-waste exposed area was associated with lower hemoglobin levels, which confirm that e-waste is a type of composite exposure source. E-waste not only contains heavy metals but also consists of organic pollutants such as polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs). These organic pollutants also inevitably affect the blood hemoglobin levels. For example, Leijs et al. showed that the total PBDEs were positively associated with hemoglobin concentrations in a cohort of mother-baby pairs (Leijs et al., 2009). Xu et al. demonstrated that both the mean level of total PBDEs and PCBs was positively correlated with levels of hemoglobin and platelets in the individuals from an e-waste dismantling area in China (Xu et al., 2015). The mechanism of e-waste on hemoglobin remains unclear and need further study, and both heavy metals and organic pollutants should be included to obtain a more accurate conclusion.

It is well known that hemoglobin, the primary transporter of oxygen, is essential for oxygen transport from the respiratory organs (i.e. lungs) to the rest of the body (i.e. tissues) (Hsia, 1998). Hassel et al. showed that there was a positive association between lung function and peak oxygen uptake in elderly (Hassel et al., 2015). Guo et al. found low levels of blood hemoglobin were related to gas exchange decline and the quantity of oxygen uptake in COPD patients (Guo et al., 2015). In addition, hemoglobin has a critical role in vascular remodeling and pulmonary hypertension (Brittain et al., 2014; Irwin et al., 2015). Previous studies demonstrated that low hemoglobin levels were associated with a higher risk for adverse cardiovascular outcomes, reduced exercise capacity and health related quality of life (HRQL) (Arant et al., 2004; Ferrari et al., 2015). However, the mechanism why lower hemoglobin has an adverse effect on lung function is still unclear. Further studies with longitudinal data are warranted to confirm and elucidate whether lower blood hemoglobin levels are associated with worse lung function.

Platelets are an important link between tissue damage/dysfunction and the inflammatory response, which plays an important role in inflammation and antimicrobial host defenses (Mirsaeidi et al., 2010; Dovizio et al., 2014). Elevated blood platelet counts and thrombocytosis are often considered a marker of inflammatory reaction of infections (Erdogan et al., 2013; Ji et al., 2015), and has been associated with increased mortality in hospitalized patients with community-acquired pneumonia (Prina et al., 2013). In the current study, the observed elevated blood platelet counts and thrombocytosis in children from Guiyu may indicate that Guiyu children may be at higher risk of infections and experienced more inflammatory reactions compared to the reference areas. Previous studies showed that chronic inflammation was associated with impaired lung function in children and in adults (Olivas-Calderon et al., 2015; Hancox et al., 2016), which may partly explain why Guiyu children had a lower lung function levels compared to those from the reference areas.

Our study has some limitations. First, a total of 206 preschool children aged 5–7 years of old was recruited in the study to ensure accurate and stabile lung function measurements, which lead to the small sample sizes. We tried to establish more cooperation with local kindergartens in Guiyu, but it was not easy to recruit more children in this e-waste exposure area, both because the local culture and the restriction of the local government. Even so, we will continue to include more local children to make a more accurate scientific conclusion. Second, the cross sectional nature of this study prevents us from drawing any conclusions about a cause-effect relation between e-waste exposure and lung function impairment. Prospective longitudinal studies are needed to assess associations between e-waste exposures and lung function decline or respiratory diseases. Third, the lower lung function in adults and non-smokers is also associated with Pb and Cd in particulate matter ($PM_{2.5}$) that comes from many sources such as traffic and industries (Cakmak et al., 2014). Although both Guiyu and the reference areas have similar traffic conditions and different industrial structure, this study fails to distinguish betwwen Pb and Cd exposure from traffic and e-waste. Finally, in addition to blood Pb and Cd, we did not investigate the joint effects of the other heavy metals such as chromium, nickel, copper, mercury, and arsenic and organic pollutants such as polycyclic aromatic hydrocarbons (PAHs), polychlorinateddibenzodioxins and dibenzofurans (PCDD/PCDFs), and polybrominateddiphenyl ethers (PBDEs) on lung function levels due to insufficient blood quantities. Advanced detection equipment is a key factor to reduce the volume of blood needed and to obtain more parameters in blood. In the next step, we should pay more attention to the joint toxicity of a variety of toxic substances from e-waste, and simultaneously measure these parameters using advanced detection equipment to obtain accurate conclusions. However, to our knowledge, this is the first study to investigate the association between living area and lung function levels, and assess whether blood Pb, Cd, hemoglobin and platelet mediate the association between living area and lung function levels in preschool children from an e-waste exposure area.

5. Conclusion

The current results showed that children from Guiyu have a risk of high levels of Pb, Cd and platelets, and low levels of hemoglobin and lung function. In addition, hemoglobin is a good predictor for lung function. Due to the strict local policy in Guiyu, the blood Pb levels in children is lower now compared to our previous studies reported in 2004, 2006, 2009, 2011, and in 2012. The concentration of blood Cd in children from Guiyu is lower now compared to those reported in 2006 and in 2009, but showed no difference with blood Cd in 2012. These findings, along with evidence from previous studies, suggest that Pb and Cd pollution continues to be a major public health problem for children in Guiyu. Broader consensus of the harm of Pb and Cd, proactive regulation and restriction of e-waste production and effective protection of individuals from e-waste are essential steps to steadily reduce blood Pb to the level under CDC guidelines, and blood Cd under suggestive level. In addition, children living in Guiyu are more likely to suffer from low hemoglobin and lung function levels, while high platelet and thrombocytocrit levels. It is also imperative to study children throughout their childhood to confirm whether e-waste pollutants such as heavy metals and plastics have a long-term adverse effect on lung function and diseases, and whether early-life Pb and Cd exposure is associated with other health outcomes later in childhood or adulthood. Multinational and multi-region research focusing on the effects of e-waste on health should be conducted to obtain accurate scientific conclusions.

Conflict of interest

All authors have read and approved this version of the article, and throughout the study, care has been taken to ensure the integrity of the work. This article or one with similar content has not been previously published or submitted to any other journal. The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.envpol.2017.07.014.

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