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$PM_{2.5}$-bound PAHs exposure linked with low plasma insulin-like growth factor 1 levels and reduced child height

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ABSTRACT

Background: Exposure to atmospheric fine particle matter ($PM_{2.5}$) pollution and the absorbed pollutants is known to contribute to numerous adverse health effects in children including to growth.
Objective: The aim of this study was to evaluate exposure levels of atmospheric $PM_{2.5}$-bound polycyclic aromatic hydrocarbons (PAHs) in an electronic waste (e-waste) polluted town, Guiyu, and to investigate the associations between $PM_{2.5}$-PAH exposure, insulin-like growth factor 1 (IGF-1) levels and child growth.
Methods: This study recruited 238 preschool children (3–6 years of age), from November to December 2017, of which 125 were from Guiyu (an e-waste area) and 113 were from Haojiang (a reference area). Levels of daily $PM_{2.5}$ and $PM_{2.5}$-bound Σ16 PAHs were assessed to calculate individual chronic daily intakes (CDIs). IGF-1 and IGF-binding protein 3 (IGFBP-3) concentrations in child plasma were also measured. The associations and further mediation effects between exposure to $PM_{2.5}$ and $PM_{2.5}$-bound PAHs, child plasma IGF-1 concentration, and child height were explored by multiple linear regression models and mediation effect analysis.
Results: Elevated atmospheric $PM_{2.5}$-bound Σ16 PAHs and $PM_{2.5}$ levels were observed in Guiyu, and this led to more individual CDIs of the exposed children than the reference (all $P < 0.001$). The median level of plasma IGF-1 in the exposed group was lower than in the reference group (91.42 ng/mL vs. 103.59 ng/mL, $P < 0.01$). IGF-1 levels were negatively correlated with CDIs of $PM_{2.5}$, but not with CDIs of $PM_{2.5}$-bound Σ16 PAHs after adjustment. An increase of 1 μg/kg of $PM_{2.5}$ intake per day was associated with a 0.012 cm reduction of child height (95% CI: −0.014, −0.009), and similarly, an elevation of 1 ng/kg of $PM_{2.5}$-bound Σ16 PAHs intake per day was associated with a 0.022 cm decrease of child height (95% CI: −0.029, −0.015), both after adjustment of several potential confounders (age, gender, family cooking oil, picky eater, eating sweet food, eating fruits or vegetables, parental education level and monthly household income). The decreased plasma IGF-1 concentration mediated 15.8% of the whole effect associated with $PM_{2.5}$ exposure and 23.9% of the whole effect associated with $PM_{2.5}$-bound Σ16 PAHs exposure on child height.
Conclusion: Exposure to atmospheric $PM_{2.5}$-bound Σ16 PAHs and $PM_{2.5}$ is negatively associated with child height, and is linked to reduced IGF-1 levels in plasma. This may suggest a causative negative role of atmospheric $PM_{2.5}$-bound exposures in child growth.

1. Introduction

Electronic waste (e-waste) is a general term for all types of discarding electronic consumer devices. The process of dismantling e-waste, including directly open-air burning, grinding and melting, and burying leads to the generation of large amounts of particulate matter, heavy metals and organic pollutants. These are eventually released into the local atmosphere, water and soil (Huo et al., 2007; Qin et al., 2019). As a major constitution of particulate matter (PM) in the atmosphere, $PM_{2.5}$ (fine PM, < 2.5 μm in aerodynamic diameter) is mainly derived from natural and anthropogenic activities. It leads to serious environmental issues, especially in e-waste recycling area (Zheng et al., 2016).

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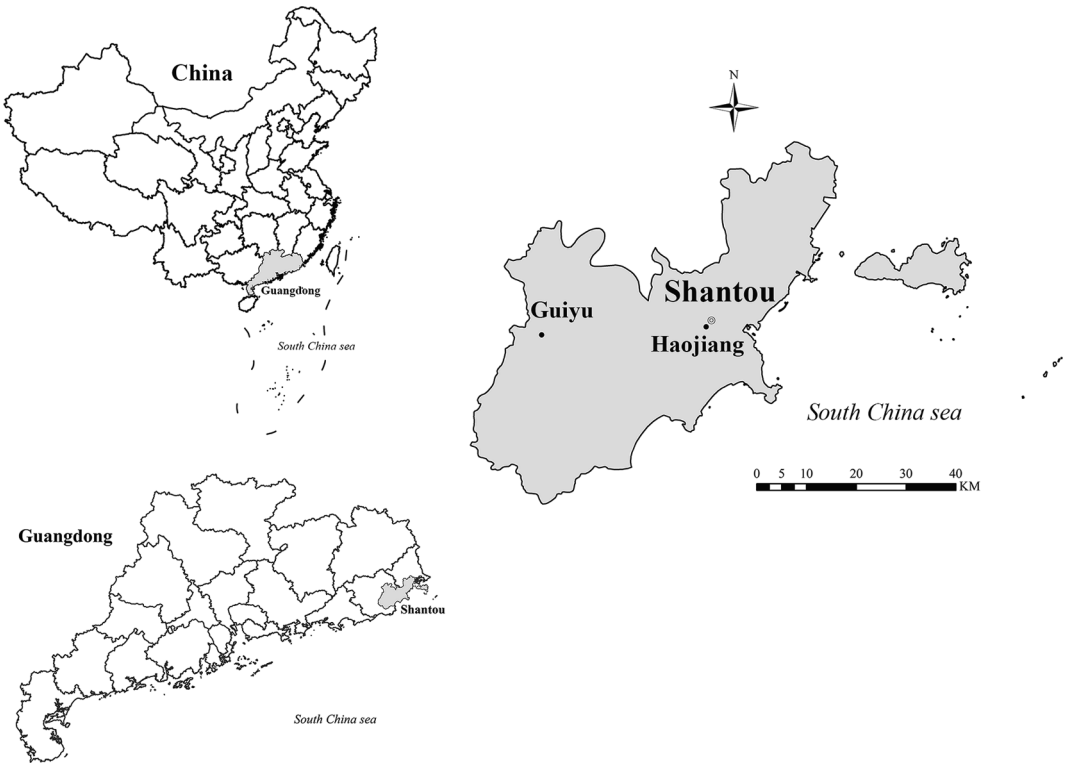

Fig. 1. Location of the study areas.

Exposure to higher concentrations of $PM_{2.5}$ in ambience contributes to numerous adverse health effects in children (Feng et al., 2016). Various other chemical pollutants, such as organic compounds and heavy metals can adhere to $PM_{2.5}$ and are eventually turned into $PM_{2.5}$-bound pollutants, posing further threats to population health (Hueglin et al., 2005; Turpin and Lim, 2001). Polycyclic aromatic hydrocarbons (PAHs) as a class of toxic organic pollutants are distributed ubiquitously in the environment. They can be transported over long distances in the atmosphere in gaseous form or bound to particulate matter (Ma et al., 2011; Yan et al., 2015). It is well known that PAHs are considered to be endocrine disruptors, so that prenatal and childhood exposure to PAHs could impede child height (Jedrychowski et al., 2015; Xu et al., 2015; Zhang et al., 2016). As $PM_{2.5}$ may behave similarly to gas molecules, it has the ability to penetrate into the human respiratory system, reaching the region of pulmonary gas exchange, and even being translocated through the lungs to the circulatory system (Kim et al., 2015; Ramírez et al., 2011). Therefore, $PM_{2.5}$ may be considered to be a concentrated source of PAHs, and subsequently, $PM_{2.5}$-bound PAHs may be considered to have more serious impact on population health. Being smaller and having a higher physiology and activity level, children are a sub-population highly susceptible to the potentially harmful effects induced by atmospheric $PM_{2.5}$ exposure (Oliveira et al., 2019; Salvi, 2007). Several recent epidemiological studies have confirmed that atmospheric pollutants can interfere with child growth, showing associations between exposure to atmospheric $PM_{2.5}$ with child height, BMI, overweight and obesity (de Bont et al., 2019; Huang et al., 2019, 2018). However, these studies only showed the correlations between atmospheric $PM_{2.5}$ and child growth. Investigations on the association analysis of atmospheric $PM_{2.5}$-bound pollutants with child growth and the potential biological mechanism under this association are still limited.

Insulin-like growth factor 1 (IGF-1) is considered to be an endocrine hormone, so that the concentration of IGF-1 in the blood can mediate linear growth (Savage, 2013). This is due mainly to IGF-1 in the bloodstream promoting the proliferation of growth plate chondrocytes, which are important in regulating linear growth (Daughaday, 2000). IGF binding protein 3 (IGFBP-3), as a major sort of IGFBP complexes, can modulate the bioavailability of free IGF-1 in human plasma, which indirectly affect the linear growth (Laron, 2001). Also, IGFBP-3 has the capability of regulating growth in an IGF-1-independent manner (Puche and Castilla-Cortazar, 2012). Large numbers of experimental animal studies and human population studies have reported that several environmental chemical pollutants, such as lead, arsenic, benzopyrene, dibenzofurans, dioxins, and polychlorinated biphenyls, can interfere with normal production of IGF-1 in children and newborns (Ahmed et al., 2013; Fleisch et al., 2013; Scarth, 2006; Tomei et al., 2004; Wang et al., 2005). However, these studies were limited to investigate the effects of toxic environmental exposure on IGF-1, which did not link IGF-1 with the linear growth.

From our previous studies, concentrations of environmental organic pollutants, such as PAHs, polychlorinated dioxins/furans, polybrominated diphenyl ethers, polychlorinated biphenyls, and heavy metals (including lead cadmium, arsenic, mercury) were apparently higher in atmospheric sample from an e-waste polluted town, Guiyu. Guiyu is famous for original and crude e-waste processing activities for over 40 years, which are commonly performed in thousands of small-scale family-run workshops (Qin et al., 2019). More importantly, adverse health outcomes related to elevated levels of $PM_{2.5}$ and $PM_{2.5}$-bound heavy metals have also been reported in this area (Qin et al., 2019; Zheng et al., 2016). Therefore, based on a preschool children cohort, the objective of this study was to estimate the ambient exposure of $PM_{2.5}$ and further $PM_{2.5}$-bound PAHs on preschool children from a typical e-waste polluted area, as well as to further investigate the associations with IGF-1 level and child height.

2. Materials and methods

2.1. Study areas and population

This study recruited two hundred and thirty-eight preschool children (3- to 6- years of age) from November to December 2017. One hundred and twenty-five participants from a kindergarten in Guiyu and another one hundred and thirteen participants from a kindergarten in

Haojiang (a place without e-waste pollution and located approximately 31.6 km to the east of Guiyu) comprised the e-waste exposed population and the reference population, respectively. The two locations are small regions in southeast coastal of China, Shantou, Guangdong province (Fig. 1). Compared to Guiyu (the exposed area), Haojiang (the reference area) is mainly with intertidal mudflat culture, tourism and marine product processing which is far less contaminated. Besides, they share a similar population density, lifestyle and cultural background, as we described previously (Dai et al. 2019). A predesigned questionnaire including information on socio-demographic characteristics and lifestyle factors was completed by the children's parent (or guardian) after their informed consent. All children included in this study were three to six years old, available for blood plasma sample analysis and without infectious, respiratory diseases or any known diseases. All protocols in this investigation were approved by the Human Ethics Committee of Shantou University Medical College (SUMC2013XM-0076), China.

2.2. Plasma biomarker analysis

Peripheral venous blood samples were obtained from each child and collected into K3-EDTA anticoagulant tubes by well-trained nurses. Each tube of blood samples was rapidly put on ice and transferred to the laboratory within two hours. After 15 min of centrifuging speed at 3000*g* in a 4 °C centrifugal machine, 100 mL of the separated plasma was stored at −70 °C until the IGF-1 and IGFBP-3 analysis.

Plasma IGF-1 and IGFBP-3 concentrations were measured by the Human IGF-1 Quantikine ELISA kit and Human IGFBP-3 Quantikine ELISA Kit (R&D Systems), respectively, following the manufacturer's instructions. All absorbance in a microplate reader was measured at 450 nm (wavelength correction set to 540 nm) and the calculation for their concentrations were based on standard curves of excellent linearity (r^2 over 0.990). Threshold sensitivities for plasma IGF-1 and IGFBP-3 were 0.056 ng/mL and 0.14 ng/mL, respectively. Assay ranges for plasma IGF-1 and IGFBP-3 were 0.1–6 ng/mL and 0.8–50 ng/mL, respectively.

2.3. Evaluation of exposure to atmospheric $PM_{2.5}$ and $PM_{2.5}$-bound PAHs pollution

2.3.1. Atmospheric $PM_{2.5}$ pollution evaluation

Air pollution data (including $PM_{2.5}$) from the local environmental monitoring station can be used to evaluate the general daily exposure of all participants living within a 15 km radius of this monitoring station (Delfino et al., 2002; Wiwatanadate, 2014). According to the address of home and kindergarten of the participated children, as well as the geographic coordinates of environmental monitoring station, all the participating children lived within an eight kilometers radius of their corresponding environmental monitoring station, as we estimated previously (Cong et al., 2018; Zhang et al., 2019). Therefore, daily $PM_{2.5}$ data of twenty-four hours from August 2017 to January 2018 in Chaonan district (covering Guiyu) and Haojiang district were collected from the National Environmental Protection Agency (NEPA) of China (http://106.37.208.233:20035/) for evaluation of local atmospheric $PM_{2.5}$ pollution. These data were determined and uploaded by the Chaonan and the Haojiang environmental monitoring stations.

2.3.2. Evaluation of $PM_{2.5}$-bound PAHs pollution

Atmospheric $PM_{2.5}$ samples were collected five times a week from October 2017 to January 2018. Each collection started at 6:00 pm of one day and finished at 4:00 pm of the next day (22 h). The collecting sites were set on the roof of 5-storey residential buildings. One was located within 50 m from an e-waste disposal site in Guiyu (23°19′32″N,116°22′25″E), and the other was situated at a reference area (without e-waste pollution) in Haojiang (23°20′20.6″N,116°40′13.7″E). $PM_{2.5}$ samples were collected using 47 mm Whatman QMA quartz filters (2.2 μm pore size; GE Inc, UK) with an American MiniVol Tactical Air Sampler (Airmetrics, Eugene, OR, USA). Before and after each sample collection, we used a flow meter to calibrate the flow rate to within 5 ± 0.5 L/min. A field blank sample was taken for every ten samples to ensure the process error was subtracted for the subsequent analysis.

One half of each of the two quartz filters with $PM_{2.5}$ samples collected in two adjacent days was cut into pieces and mixed well. The pieces were ultrasonically extracted three times (20 min each time) by addition of 10 mL of a 2:2:1 (volume ratio) hexane/dichloromethane/acetone solution in an ultrasonic cleaner. Ultrasonic extracts were filtered through a multilayer silica gel column (including 1 g anhydrous sodium sulfate; 12 g neutral silica, activated at 180 °C for 12 h before use; 6 g neutral alumina, activated at 250 °C for 12 h) and eluted with 30 mL hexane/dichloromethane (3:7 v/v). The elution was concentrated in the water bath to approximately 2 mL, and then evaporated to dryness using a nitrogen stream. After that, 50 μL hexane was poured in for re-solubilization. A PAH standard mixture solution comprised of sixteen United States Environmental Protection Agency (U.S. EPA) priority PAH congeners, namely acenaphthene, acenaphthylene, anthracene, benzo[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene, benzo[g,h,i]perylene, benzo[k]fluoranthene, chrysene, dibenzo[a,h]anthracene, fluoranthene, fluorene, indeno[1,2,3-c,d] pyrene, naphthalene, pyrene, and phenanthrene, were purchased from o2si (Charleston, SC, USA). The working standard solution was prepared avoiding light exposure, each stock solution was put into a brown volumetric flask and mixed well, stored at 4 °C until use. Quantitative analysis was performed using an isotopic internal standard method. Fifty microliters of internal standard (1 ppm) was added to the above 50 μL resolubilized solution (containing samples), and then they were ultimately analyzed using an Agilent 7890A-5975C gas chromatography-mass spectrometry (GC/MS, Agilent Technologies, America) with an electron ionization (EI) ion source. Solid phase extraction (SPE) cartridges (Supelclean™, LC-18, USA) were utilized for cleanup. The calibration curves displayed excellent linearity (r^2 ranged from 0.996 to 0.999), relative standard deviation (RSD%) was within 0.3%–15.7% and recoveries for surrogate standard ranged from 76% to 114%.

2.3.3. Evaluation of individual daily exposures of atmospheric $PM_{2.5}$ and $PM_{2.5}$-bound PAHs

The guidelines for population health risk assessment of respiratory exposure to atmospheric $PM_{2.5}$ and pollutants in $PM_{2.5}$ have been detailed in previous investigations (Betha et al., 2013; Zhang et al., 2019; Zheng et al., 2016). This assessment depends mainly on the daily intake of the air pollutants via the respiratory system in each individual, and their body weight. Based on this method, we estimated the daily child exposures to $PM_{2.5}$ and $PM_{2.5}$-bound PAHs through calculating the individual chronic daily intake (CDI) of the air pollutants. In brief, we used this formula: individual CDI = (TD × IR)/BW; TD = C × E. In the formula, TD is the total dose ($ng{\cdot}m^{-3}$) of the exposure; IR represents the inhalation rate ($m^3{\cdot}day^{-1}$) of each individual; BW is the body weight (kg); C represents the median value of the daily $PM_{2.5}$ level (the exposure time covering three months before and one month after the $PM_{2.5}$ sample collection in this study) or total $PM_{2.5}$-bound PAHs concentrations in the $PM_{2.5}$ samples, and E describes the deposition fraction of particles by size. The value of E is deducted and calculated according to a computer-based model, LUDEP 2.07, while other parameters in this equation were obtained from the reference for 5-year-old child, as detailed before (ICRP, 1994; Zhang et al., 2019; Zheng et al., 2016). Additionally, daily time of outdoor exposure in this model were utilized to estimate the corresponding child IR according to the estimates of child outdoor playing time (Zhang et al., 2019; Zheng et al., 2016).

2.4. Outcome assessment

Physical measurements, including the height and weight of children

were performed and recorded by trained staff according to a standard protocol. Height was measured in centimeters (cm) and weight in kilograms (kg), all data were exacted to one decimal point. Body mass index (BMI) was calculated using the standard formula: BMI (kg/m^2) = weight (kg)/[height (m)]^2.

2.5. Covariates

Data on socio-demographic characteristics and lifestyle factors were obtained from the questionnaire finished by the children's guardians. Since described in several studies that smoking, dietary and lifestyle factors can affect IGF-1 and IGFBP-3 levels (Baibas et al., 2003; DeLellis et al., 2004; Kaklamani et al., 1999), these included questions on child eating and behavior habits, dwelling environment and disease situations over the past month of the participated child, in addition to maternal educational level, family member daily smoking and monthly household income. Particularly, to evaluate child eating habits, the type of family cooking oil (mainly animal oil; mainly plant oil; both animal and plant oil; rarely use of cooking oil), child is a picky eater (yes or not), the frequency of child eating sweet food and eating fruits or vegetables (everyday; 1–3 times a week; 1–3 times a month; < 1 time a month) as potential confounders were detailed in the questionnaire.

2.6. Statistical analysis

Daily $PM_{2.5}$, $PM_{2.5}$-bound PAHs and plasma biomarker concentrations were presented as mean ± standard deviation (SD) or median [interquartile range (IQR): the 25th percentile, the 75th percentile] as appropriate, while the composition ratios of categorical variables were expressed as percentage. Comparative analysis of the differences in continuous variables between the two study groups were analysed with Mann-Whitney *U* test and independent-sample t tests as appropriate, whereas Pearson chi-square was utilized for categorical variables. Spearman rank correlation analysis was applied to explore the correlations between individual CDIs of $PM_{2.5}$ and $PM_{2.5}$-bound PAHs and their potentially influencing factors. Multivariable linear regression models and the models of adjustment for confounders of age, gender, height, weight, BMI, family cooking oil, picky eater, eating sweet food, eating fruits or vegetables, maternal education levels and family member daily cigarette consumption were used to evaluate associations of individual CDIs of $PM_{2.5}$ and $PM_{2.5}$-bound Σ16 PAHs with child plasma IGF-1 and IGFBP-3 concentrations, as well as the associations of child plasma IGF-1 and IGFBP-3 concentrations with child height. A causal mediation model was further applied using the testing approach proposed by Baron et al. to assess the child plasma IGF-1 levels on the associations between $PM_{2.5}$ CDIs, CDIs of $PM_{2.5}$-bound Σ16 PAHs, and child height with confounding factors adjusted (Baron and Kenny, 1986). Atmospheric exposure, growth outcomes and covariates with missing data were cases-listwise excluded and not imputed in the above linear regression and mediation models. All statistical analyses were performed using SPSS 20.0 for Windows (Chicago, IL, USA) and GraphPad Prism 5.0 (GraphPad, CA). Statistical significance test cutoff was 0.05 for a two-tailed test.

3. Results

3.1. General characteristics of the two study populations

A total of two hundred and thirty-eight preschool children participated in this investigation. Table 1 lists characteristics of the participants from the reference group (n = 113) and exposed group (n = 125). The mean age of the exposed group was 4.7 ± 0.7 years and in the reference group, Haojiang, was 4.8 years (SD ± 0.7). Compared with the reference group, children in the exposed group were shorter and weighted less (104.18 cm vs.108.56 cm, $P < 0.001$ and 16.57 kg vs. 18.21 kg, $P < 0.001$). No significant difference was found for age, gender ratio, or BMI between children in Guiyu and Haojiang ($P > 0.05$). However, the two study groups had different age distributions and eating habits (such as household cooking oil consumption, eating sweets, fruits or vegetables and picky eating) ($P < 0.001$). Moreover, children of the two groups played and lived in different surroundings and conditions (such as open windows in the living place, using an air-conditioner with the window closed, outdoor playing time, e-waste pollution within 50 m away from residence, distance of residence away from road and family member daily smoking) ($P < 0.01$). In comparison with the reference group, parents of the exposed children had a lower education level and less household income per month ($P < 0.01$).

3.2. Atmospheric $PM_{2.5}$ pollution, concentration of $PM_{2.5}$-bound Σ16 PAHs and related factors influencing individual CDI

In Fig. 2, the distribution of atmospheric $PM_{2.5}$ pollution and total PAH exposure in $PM_{2.5}$ between the e-waste-polluted area and reference area are compared. Furthermore, it compares the chronic daily intake (CDI) of individual children in the two groups. The median concentration for the exposed area is significantly elevated in comparison with the reference area (33.43 μg/m^3 vs. 23.50 μg/m^3, $P < 0.001$) (Fig. 2A, Table S1). The median $PM_{2.5}$-bound Σ16 PAH levels of the exposed area was 7.28 (IQR: 5.03, 11.25) ng/m^3 which was two point nine times higher than the reference area (2.47 (IQR: 1.34, 4.81) ng/m^3) ($P < 0.001$) (Fig. 2B, Table S1). Likewise, the median individual CDI of $PM_{2.5}$ in the exposed children was largely increased when compared to the reference children (1186.76 μg/kg·day vs. 794.45 μg/kg·day, $P < 0.001$) (Fig. 2C, Table S1). Compared to reference children, the median individual CDI of $PM_{2.5}$-bound Σ16 PAH in exposed children has also significantly increased (261.70 ng/kg·day vs. 81.66 ng/kg·day, $P < 0.001$) (Fig. 2D, Table S1). Additionally, Spearman correlation analysis indicated that individual CDI of $PM_{2.5}$ was positively correlated to open windows in living place, using an air-conditioner with the windows closed, having e-waste pollution within 50 m away from the residence and family member daily smoking (r = 0.262, 0.233, 0.336 and 0.189; respectively, all $P < 0.01$), whereas negative correlations were found between individual CDI of $PM_{2.5}$ and child outdoor playing time and distance of residence away from the road (r = −0.158, $P < 0.05$; r = −0.430, $P < 0.001$, respectively) (Table 2). Likewise, individual CDI of $PM_{2.5}$-bound Σ16 PAHs was also positively correlated with open windows in the living place, using an air-conditioner with the windows closed, having e-waste pollution within 50 m away from the residence and family member daily smoking (r = 0.265, 0.247, 0.348 and 0.195, respectively, all $P < 0.001$), while it negatively correlated to child outdoor playing time and distance of residence away from the road (r = −0.179, −0.450; both $P < 0.01$, respectively) (Table 2).

3.3. Plasma IGF-1, IGFBP-3 concentrations and associations with individual CDIs of $PM_{2.5}$ and $PM_{2.5}$-bound Σ16 PAHs

As shown in Fig. 3A, the plasma IGF-1 concentration of exposed children was significantly lower than the reference group (median: 103.59 ng/mL vs. 91.42 ng/mL, Table S2, $P < 0.01$). When the comparisons were further stratified by age group, plasma IGF-1 levels in children of age 4 group (median: 85.48 vs. 97.90 ng/mL, $P < 0.01$) and age 6 group (median: 93.93 vs. 148.56 ng/mL, $P < 0.05$) were reduced significantly in the exposed area (Fig. 3A Table S2). However, there was no significant difference in child plasma IGFBP-3 levels even if the data was stratified by age group, between the two groups (Fig. 3B, Table S2, $P > 0.05$).

Multivariable linear regression analysis indicated that individual $PM_{2.5}$ CDIs were negatively associated with plasma IGF-1 levels [B (95% CI) = −0.041 (−0.056, −0.026), $P < 0.001$] in an unadjusted model (Table 3). After further adjustment for age, gender, height,

Table 1
Demographic characteristics of preschool children in the reference area (Haojiang) and the exposed area (Guiyu).

Characteristics	Reference group (n = 113)	Exposed group (n = 125)	Statistics	*P*-value
Age	4.8 ± 0.8	4.7 ± 0.7	t = 0.756	0.450 [a]
Age group [n (%)]			χ^2 = 10.197	0.017[b]
3- year-old	28 (24.8)	18 (14.5)		
4- year-old	36 (31.9)	64 (51.6)		
5- year-old	40 (35.4)	33 (26.6)		
6- year-old	9 (8.0)	9 (7.3)		
Gender (boys/girls)	62/51	64/61	χ^2 = 0.190	0.663[b]
Height (cm)	108.56 ± 6.64	104.18 ± 6.18	t = 4.931	0.000 [a]
Weight (kg)	18.21 ± 2.77	16.57 ± 2.18	t = 5.075	0.000 [a]
BMI (body mass index, kg/m^2)	15.40 ± 1.35	15.14 ± 1.16	t = 1.547	0.123 [a]
Household cooking oil consumption [n (%)]			χ^2 = 37.72	0.000[b]
mainly animal oil	4 (3.5)	15 (12.1)		
mainly plant oil	72 (63.7)	31 (25.0)		
both animal and plant oil	37 (32.7)	76 (61.3)		
rarely cooking oil	0 (0.0)	2 (1.6)		
Picky eater (yes/no)	64/49	45/75	χ^2 = 7.810	0.005[b]
Eating sweet food [n (%)]			χ^2 = 27.809	0.000[b]
everyday	10 (8.8)	44 (35.2)		
1–3 times a week	70 (61.9)	66 (52.8)		
1–3 times a month	30 (26.5)	14 (11.2)		
< 1 time a month	3 (2.7)	1 (0.8)		
Eating fruits or vegetables [n (%)]			χ^2 = 26.948	0.000[b]
everyday	88 (77.9)	58 (46.4)		
1–3 times a week	22 (19.5)	56 (44.8)		
1–3 times a month	3 (2.7)	5 (4.0)		
< 1 time a month	0 (0.0)	6 (4.8)		
Family member daily smoking [n (%)]			χ^2 = 14.515	0.006[b]
Non-smoking	53 (46.9)	34 (27.6)		
−2 cigarettes	16 (14.2)	11 (8.9)		
−10 cigarettes	18 (15.9)	31 (25.2)		
−20 cigarettes	20 (17.7)	33 (26.8)		
> 20 cigarettes	6 (5.3%)	14 (11.4)		
Open windows in the living place [n (%)]			χ^2 = 19.736	0.000[b]
often	111 (1 0 0)	103 (83.7)		
sometimes	0 (0)	19 (15.4)		
never	0 (0)	1 (0.8)		
Using an air-conditioner with the windows closed (yes/no)	88/10	67/45	χ^2 = 22.767	0.000[b]
Child outdoor playing time [n (%), hour]			χ^2 = 56.055	0.000[b]
≤0.5	3 (2.7)	19 (15.6)		
−1	25 (22.1)	41 (33.6)		
−2	47 (41.6)	35 (28.7)		
−3	19 (16.8)	21 (17.2)		
> 3	19 (16.8)	6 (4.9)		
E-waste pollution within 50 m away from the residence (yes/no)	112/1	81/39	χ^2 = 38.713	0.000[b]
Distance of residence away from the road [n (%), m]			χ^2 = 85.443	0.000[b]
< 10	4 (3.5)	56 (46.3)		
−50	22 (19.5)	29 (24.0)		
−100	23 (20.4)	26 (21.5)		
> 100	64 (56.6)	10 (8.2)		
Maternal educational level [n (%)]			χ^2 = 50.497	0.000[b]
Middle school or lower	30 (26.6)	89 (71.8)		
Secondary school	17 (15.0)	12 (9.7)		
High school	18 (15.9)	6 (4.8)		
College/University	48 (42.5)	17 (13.7)		
Monthly household income [n (%), yuan]			χ^2 = 14.114	0.003[b]
< 3000	14 (12.4)	25 (21.7)		
−4500	17 (15.0)	24 (20.9)		
−6000	19 (16.8)	30 (26.1)		
> 6000	63 (55.8)	36 (31.3)		

Values are expressed as mean ± SD or percentage.
[a] Analyzed by Independent-sample *t*-test.
[b] Analyzed by Pearson chi-square test.

weight, BMI, family cooking oil, picky eater, eating sweet food, eating fruits or vegetables, maternal education levels and family member daily cigarette consumption, individual $PM_{2.5}$ CDIs remained negatively associated with plasma IGF-1 levels [B (95% CI) = −0.025 (−0.048, −0.003), $P < 0.05$]. Similarly, more individual CDIs of $PM_{2.5}$-bound ΣPAHs were associated with the reduced plasma IGF-1 levels in unadjusted regression analysis [B (95% CI) = −0.092 (−0.133, −0.050), $P < 0.001$]. However, in an adjusted linear regression model, only the trend that was negative associated between the CDIs of $PM_{2.5}$-bound Σ16 PAHs and plasma IGF-1 levels [B (95% CI) = −0.049 (−0.102, 0.005), $P = 0.073 < 0.1$].

3.4. Mediation analysis of child plasma IGF-1 levels on the association between individual $PM_{2.5}$ CDIs, CDIs of $PM_{2.5}$-bound Σ16 PAHs and child height

Mediation analysis of child plasma IGF-1 levels on the association between the CDIs of $PM_{2.5}$ and $PM_{2.5}$-bound Σ16 PAHs and child height

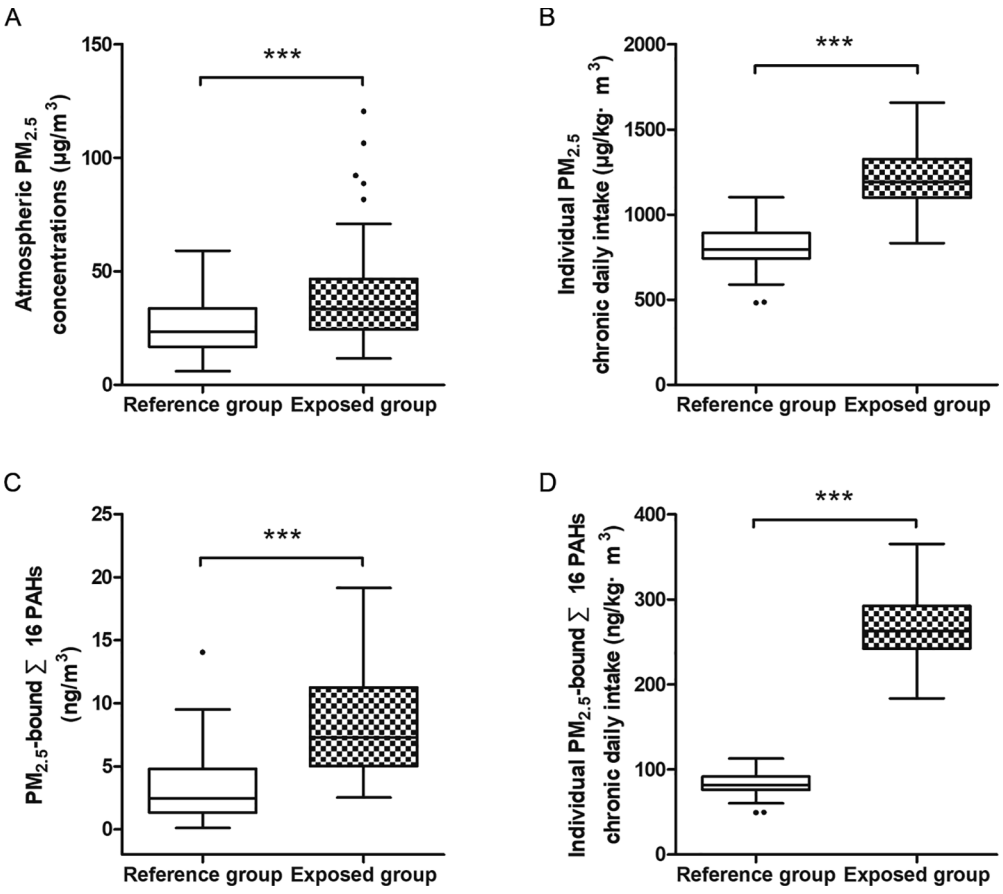

Fig. 2. Comparisons of atmospheric $PM_{2.5}$ and $PM_{2.5}$-bound Σ16 PAHs concentrations in two study areas, individual chronic daily intakes of $PM_{2.5}$ and $PM_{2.5}$-bound Σ16 PAHs in preschool children from an e-waste recycling area (exposed group) and a reference area (reference group). Figure A-D, analyzed by the Mann-Whitney *U* test, ***Significant at $P < 0.001$ and data showed as median (IQR).

Table 2
Spearman correlation analysis between individual CDIs of $PM_{2.5}$ and $PM_{2.5}$-bound ΣPAHs and their influencing factors.

Investigated factors	CDI ($PM_{2.5}$)		CDI ($PM_{2.5}$-bound ΣPAHs)	
	r	*P*	r	*P*
Family member daily smoking	0.189	0.004	0.195	0.003
Open windows in the living place	0.262	0.000	0.265	0.000
Using an air-conditioner with the windows closed	0.233	0.001	0.247	0.000
Child outdoor playing time	−0.158	0.016	−0.179	0.006
E-waste pollution within 50 m away from the residence	0.336	0.000	0.348	0.000
Distance of residence away from the road	−0.430	0.000	−0.450	0.000

are shown in Fig. 4A and B, after adjustment of potential confounders (age, gender, family cooking oil, picky eater, eating sweet food, eating fruits or vegetables, parental education level and monthly household income). Each 1 ng/mL plasma IGF-1 level increase was associated with an elevation of 0.106 cm in height (95% CI: 0.081, 0.131). A 1 μg/kg·day $PM_{2.5}$ increase was associated with a reduction of 0.012 cm in height (95% CI: −0.014, −0.009) and a 1 ng/kg·day elevation of Σ16 PAHs in $PM_{2.5}$ was correlated with a 0.022 cm decrease in height (95% CI: −0.029, −0.015). A decreased IGF-1 concentration mediated 15.8% of the whole effect associated with $PM_{2.5}$ exposure on child height, as well as mediated 23.9% of the whole effect associated with $PM_{2.5}$-bound PAHs exposure on child height.

4. Discussion

This study explored the effects of exposure to atmospheric $PM_{2.5}$ and $PM_{2.5}$-bound of a total of 16 PAHs in a typical e-waste recycling area on preschool child growth. We observed several important findings from this study. First, preschool children living in the e-waste recycling area have higher concentrations of individual CDIs of air pollutants (both $PM_{2.5}$ and $PM_{2.5}$-bound PAHs), which are negatively associated with child height. Exposure to $PM_{2.5}$-bound PAHs has more serious effects on child growth. Second, a mediation effect analysis indicated that these negative associations are both mediated by a lower plasma IGF-1 concentration. Our present study, to the best of our knowledge, is the first to emphasize the importance of decreased plasma IGF-1 level on the association of exposure to atmospheric $PM_{2.5}$ (particularly $PM_{2.5}$-bound PAHs) with child growth.

The atmospheric $PM_{2.5}$ exposure level in the exposed area was much higher than in the reference area. This is consistent with the results from our prior studies (Cong et al., 2018; Zeng et al., 2016; Zhang et al., 2019; Zheng et al., 2016). Moreover, the median $PM_{2.5}$ concentrations in Guiyu town exceeded the normal standards of atmospheric $PM_{2.5}$ (25 μg/m^3 24-hour mean) reported in World Health Organization at 2018, while these did not exceed in the reference area. We further observed an approximately three-fold higher median concentration of $PM_{2.5}$-bound Σ16 PAHs (regarded as priority pollutants by the U.S. EPA) in the e-waste-exposed area when compared with the reference area. This result indicates that more PAHs are absorbed in $PM_{2.5}$ in the exposed area than in the reference area, which is in line with the higher levels of PAH pollution observed in this environment (Xu et al., 2016, 2015; Zheng et al., 2019). These higher levels of atmospheric pollutants in Guiyu town could be explained by the use of processes including grinding and melting, open-air burning, residue and ash dumping in e-waste dismantling and recycling sectors, which could promote greater particle emissions into the air and deteriorate the ambient atmosphere. Guiyu children with heavier burdens for chronic daily intake of $PM_{2.5}$ and $PM_{2.5}$-bound PAHs could also be a reflection of the poor residential

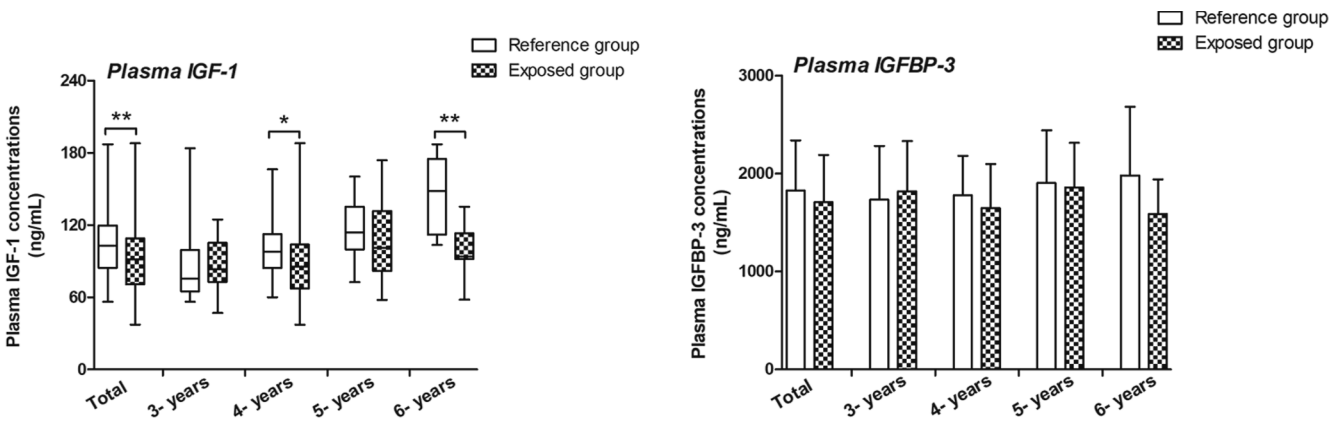

Fig. 3. Comparisons of plasma levels of IGF-1 and IGFBP3 in the e-waste exposed children and the reference children. Figure A, analyzed by the Mann-Whitney *U* test, **Significant at $P < 0.01$, *Significant at $P < 0.05$, and data showed as median (IQR); Figure B, analyzed by the Independent-sample *t*-test, data presented as mean ± SD.

environment and lifestyle, which may enhance the possibility of atmospheric exposure.

A Spanish study found that exposure to atmospheric $PM_{2.5}$ is associated with higher odds of overweight or obesity in childhood, which indicates a negative impact of the $PM_{2.5}$ exposure on child growth (de Bont et al., 2019). Recent studies also indicate air pollution containing NO_2, $PM_{2.5\text{-}10}$ and PM_{10} mass lead to higher levels of osteocalcin and C-terminal telopeptide of type I collagen (bone turnover markers) in serum of the 10 year-old children, which could influence child bone development (Liu et al., 2015). The results of the present study showed that higher exposures of both atmospheric $PM_{2.5}$ and $PM_{2.5}$-bound PAHs were negatively associated with child physical growth, which is not only in agreement with the results from the childhood exposure study, but also is supported by the child height being negatively associated with their peripheral blood Σ16 PAH levels (after adjustment for age, gender, and child milk products consumption) in our previous investigation (Xu et al., 2015). Although the specific biological mechanisms concerning exposure to atmospheric $PM_{2.5}$ and further $PM_{2.5}$-bound PAHs on child growth are largely unknown, some reasonable mechanisms can be hypothesized. As IGF-1 is a major regulator of childhood growth, the possibility exists that environmental contaminants such as atmospheric $PM_{2.5}$ could interrupt the growth hormone (GH)/IGF-1 axis. Results from the present study showed that children from the e-waste-exposed group experienced higher exposure levels of atmospheric $PM_{2.5}$ and also had lower IGF-1 concentrations in their plasma, while the plasma IGFBP-3 concentrations did not vary in two groups. Furthermore, our study reported that elevated concentrations of atmospheric $PM_{2.5}$ was associated with lower child plasma IGF-1 (after adjustment for potential confounders). However, there was no significant association between exposure to atmospheric $PM_{2.5}$ and child plasma IGFBP-3 level (data not shown). This may indicate a regulatory role of IGF-1 in atmospheric $PM_{2.5}$ exposure-associated growth impairment of preschool children.

As more toxic chemical substances are dispersed in the air of the e-waste dismantling areas, more environmental poisonous substances (such as the heavy metals and organic pollutants) could bound to $PM_{2.5}$ in the atmosphere. In this case, exposure to atmospheric $PM_{2.5}$ represents a mixed exposure of pollutants. Several human population studies have indicated that these environmental chemical pollutants could interrupt tissues or organs to abnormally synthesize and secrete IGF-1 or its gene expression to regulate growth and development via the IGF axis. Reduction of IGF-1 levels in children with growth hormone deficiency is reported to be associated with blood lead concentration (Xu et al., 2014). Arsenic exposure is correlated to child growth impairment, which can be partly mediated through lower the IGF-1 levels (Ahmed et al., 2013). Childhood exposure to phthalates is negatively associated with IGF-1 and child growth (Boas et al., 2010; Wu et al., 2017). High levels of PAH benzo-α-pyrene (BαP) in human placental trophoblast cells leads to reduction of IGF-1 expression, and BαP could directly affect these placental trophoblast cells and contribute to intrauterine growth restriction or other developmental abnormalities and diseases (Fadiel et al., 2013). In the present study, we noticed that elevated levels of total $PM_{2.5}$-bound (a total of 16 PAHs, including BαP) correlated with lower IGF-1 levels, although after adjusting for the confounders of age, sex, smoking status, smoking, diet and lifestyle, there was only a negative trend in the association. In addition, these higher exposures were directly correlated with the decrease in child height, respectively. Furthermore, a birth cohort study reported that exposure to $PM_{2.5}$ *in utero* is positively correlated to the dysregulated methylation of the critical genes involved circadian pathway, which

Table 3
Associations of individual CDI ($PM_{2.5}$), CDI ($PM_{2.5}$-bound ΣPAHs) with plasma IGF-1 levels in preschool children.

Plasma IGF-1	Individual CDI ($PM_{2.5}$)		*P*-value	Individual CDI ($PM_{2.5}$-bound ΣPAHs)		*P*-value
	B (95% CI)	β		B (95% CI)	β	
Model 1	−0.041 (−0.056, −0.026)	−0.350	0.000	−0.092 (−0.133, −0.050)	−0.285	0.000
Model 2	−0.022 (−0.042, −0.002)	−0.185	0.028	−0.041 (−0.084, 0.002)	−0.127	0.064
Model 3	−0.026 (−0.048, −0.004)	−0.212	0.021	−0.050 (−0.100, 0.000)	−0.155	0.049
Model 4	−0.025 (−0.048, −0.003)	−0.209	0.029	−0.049 (−0.102, 0.005)	−0.151	0.073

Model 1: data analysis without adjustment.
Model 2: data analysis with adjustment of age, gender, height, weight and BMI.
Model 3: data analysis with adjustment of age, gender, height, weight, BMI, family cooking oil, picky eating, eating sweets, eating fruits or vegetables.
Model 4: data analysis with adjustment of age, gender, height, weight, BMI, family cooking oil, picky eating, eating sweets, eating fruits or vegetables, maternal education levels and family member daily cigarette consumption.
Note: IGF-1, insulin growth factor 1; B, unstandardized coefficient; CI, confidence interval; β, standardized coefficient.

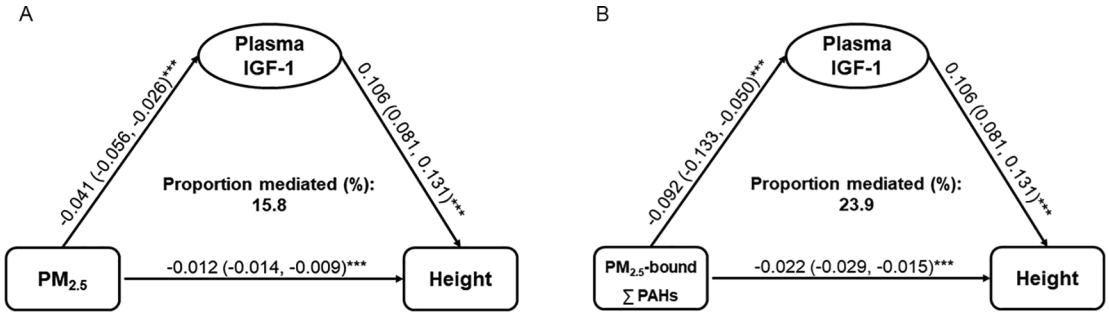

Fig. 4. Mediation effect assessments of plasma IGF-1 level on the association of exposure to atmospheric $PM_{2.5}$ and $PM_{2.5}$-bound PAHs with child height. Figure A, showed mediation effect of plasma IGF-1 level on the association of exposure to atmospheric $PM_{2.5}$ with child height, ***$P < 0.001$; Figure B, showed mediation effect of plasma IGF-1 level on the association of exposure to $PM_{2.5}$-bound PAHs with child height, ***$P < 0.001$.

reveals a potential biological mechanism for associations between this exposure and fetal growth restriction (Nawrot et al., 2018). However, another analogous study found that maternal exposure to $PM_{2.5}$ during pregnancy is associated with reduced fetal growth, which is mediated by the elevated levels of hemoglobin in mothers (Liao et al., 2019). Although neonatal growth could be totally different from childhood growth, these studies did not investigate in depth the potential mechanism linking $PM_{2.5}$ exposure with the growth. The results of mediation analysis in the present study showed that the decreased IGF-1 concentration could mediate 15.8% of the whole effect associated with atmospheric $PM_{2.5}$ exposure, but 23.9% of the whole effect associated with $PM_{2.5}$-bound PAHs exposure on child height. Hence, in our study, higher concentrations of $PM_{2.5}$ in atmosphere (particularly $PM_{2.5}$-bound PAHs) decreases the IGF-1 levels (without varying IGFBP-3 levels) in peripheral blood which could negatively regulate the GH/IGF-1 axis. Then, less IGF-1 is expressed in the growth plate and fewer growth plate chondrocytes proliferate, which ultimately contributes to reduced child height (Sanderson, 2014).

There are several strengths in this study. Firstly, we measured the levels of a total of 16 PAHs in $PM_{2.5}$ and combined this data with the daily $PM_{2.5}$ data from the NEPA of China to better assess the adverse effects of $PM_{2.5}$ exposure on preschool child health in a typical e-waste recycling area. Secondly, we further investigated the mediation role of plasma IGF-1 level on the association between exposure to total $PM_{2.5}$-bound PAHs (not just atmospheric $PM_{2.5}$ exposure in general) and child growth. Thirdly, we measured inner biomarkers to evaluate the ambient exposures which was more accurate than the association studies merely focused on the outer monitoring data.

Some limitations of this study still need to be considered. Firstly, the study sample size was relatively small, and accurate individual exposures of $PM_{2.5}$ and $PM_{2.5}$-bound PAHs using personal monitoring equipment or sensors were difficult to obtain because of the age of the study objects. Secondly, our study is fundamentally a cross-sectional study, although casual mediation effects were observed, and longitudinal and large-scale population studies investigating the exposure effects of atmospheric $PM_{2.5}$ and the bound pollutants in $PM_{2.5}$ on growth are needed. Thirdly, other chemical compounds such as heavy metals and other organic pollutants could also bound to $PM_{2.5}$ and could be possible confounders. This may partly affect the observed associations in this study.

5. Conclusions

Our study shows higher concentrations of $PM_{2.5}$, as well as of $PM_{2.5}$-bound Σ16 PAHs in the atmosphere of the e-waste polluted area. This may lead to a heavier burden of CDIs in preschool children from this area. Negative associations were found between exposure to atmospheric $PM_{2.5}$-bound Σ16 PAHs, $PM_{2.5}$ and child height, and are linked to reduced IGF-1 levels in plasma. This may suggest a causative negative role of atmospheric $PM_{2.5}$-bound exposures in child growth. Future research is needed to validate the findings in the large-scale population with consideration of the atmospheric exposures in different environments.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Contributions

ZZ, XH and XX conceived and designed research; ZZ and CW performed experiments; ZZ and QW conducted the statistical analysis; ZZ prepared figures and tables; ZZ drafted manuscript; XH, QW, MNH and XX edited and revised manuscript; All authors approved final version of manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105660.

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