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Maternal urinary metabolites of PAHs and its association with adverse birth outcomes in an intensive e-waste recycling area

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ABSTRACT

Polycyclic aromatic hydrocarbons (PAHs) are well-known carcinogenic and endocrine disrupting chemicals that have been concerned over the past few decades. We aimed to determine the hydroxylated PAH (OHPAH) metabolite concentrations in maternal urine collected from the e-waste-contaminated area of Guiyu and the reference area of Haojiang, China, and to evaluate their health effects on birth outcomes. The median ΣOHPAH concentration was 6.87 μg/g creatinine from Guiyu, and 3.90 μg/g creatinine from Haojiang. 2-OHNap and 1-OHPyr were the predominant metabolites. Residence in Guiyu and recycling in houses were associated with elevated 2-OHNap and 1-OHPyr. Standardized mean difference revealed that compared to low PAH metabolite levels in the first quartile, high PAH metabolite levels in the fourth quartile especially for 1-OHPyr, ΣOHPAHs and sometimes hydroxylphenanthrene compounds, presented a reduced size in birth outcomes (overall SMD: −0.09; 95% CI: −0.15, −0.03), including head circumference, BMI and Apgar 1 score, and increased size in height. After adjusting for confounders in regression models, an interquartile increase in ΣOHPAHs was associated with a decrease of 234.56 g in weight (95% CI: −452.00, −17.13), 1.72 cm in head circumference (95% CI: −2.96, −0.48), 1.06 kg/m^2 in BMI (95% CI: −1.82, −0.31) and 0.42 in Apgar 1 score (95% CI: −0.66, −0.18), respectively. These findings suggest high exposure to PAHs during pregnancy in e-waste areas, posing a potential threat to neonatal development, which likely can be attributed to direct e-waste recycling activities. Ongoing studies should be continued to monitor human exposure and health, in particular for vulnerable individuals in e-waste-polluted areas.

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs), composed of two or more fused aromatic rings, are typical semi-volatile endocrine disrupting-chemicals emitted from diverse sources, and resulting from incomplete burning of a variety of objects, including fuels, garbage, or other organic substances, such as tobacco and plant material, forest fires and volcanic eruptions (Cathey et al., 2018). Being highly hydrophobic and of low solubility, PAHs are difficult to degrade and ubiquitously exist in the environment (Dat and Chang, 2017). People are usually exposed by dietary intake and inhalation (Liu et al., 2017). Evidence shows that varying PAH levels are found in multiple environmental and human matrixes, such as water (Zhang et al., 2017a,b), air (Luo et al., 2015), dust (Liu et al., 2016), soil (Nishimura et al., 2017; Zhang et al., 2018), fruits and vegetables (Paris et al., 2018), and human blood, placenta, breast milk and urine (Xu et al., 2015; Yu et al., 2015; Zhang et al., 2017a,b; Yang et al., 2018). Internal PAHs are easily metabolized into more hydrophilic and polar metabolites that pass out of the body in the urine and feces (Yang et al., 2018). Their widespread existence and intermediate byproducts, mostly the formation of PAH-DNA adducts, have aroused much concern, since numerous studies in vitro and in vivo have shown specific mixtures of PAHs to be cancer-causing agents (Baird et al., 2005; Pratt et al., 2011; Ewa and Danuta, 2017).

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Electronic waste (e-waste) has been recently aroused global concern, with an estimation to be 41.8 million tonnes in 2014 and up to 65.4 million tonnes by 2017 (Heacock et al., 2016; Zeng et al., 2017a,b). China and the United States are the largest producers of e-waste, twice the level of production than other individually industrialized countries (Chen et al., 2011; Wang et al., 2016). Guiyu, located in southern China, is one of the largest e-waste destinations in the world (Zeng et al., 2017a,b). The informal recycling of e-waste, involving burning of wires to recover copper, heating of circuit boards over honeycombed coal blocks, and using acid chemical stripping agents to recover gold and other metals, releases large amounts of toxicants into local environment through multiple pathways, potentially impacting human health and the ecosystem (Zeng et al., 2016). We previously found that soil samples from two e-waste areas, in China and Nigeria, are highly contaminated with toxic PAHs that are associated with concentration-dependent increases in DNA damage in human peripheral blood lymphocytes (Alabi et al., 2012). These results provide clues for the existence of a considerable amount of toxic PAH residues in the local surroundings, resulting in potential health risks in folks living there, particularly for individuals sensitive to toxicants.

Extensive investigations have been carried out to assess human PAH exposure sources and their health outcomes. Due to the diversity and fluctuating concentrations of PAHs, efforts have been directed to characterize single or multiple metabolites as PAH exposure biomarkers. Urine has been recognized as an effective biological matrix for human exposure to PAHs in the environment (Bortey-Sam et al., 2017). Urinary 1-hydroxypyrene (1-OHPyr) is associated with genotoxicity and can serve as a biomarker for internal exposure to PAHs (Talaska et al., 2014; de Oliveira et al., 2017). Urinary 1-OHPyr is associated with increased malondialdehyde and 8-hydroxyl-deoxyguanosine, indicative of oxidative stress, in workers and general population (Al-Saleh et al., 2013; Kuang et al., 2013; Li et al., 2016; Lu et al., 2016). Although studies have associated prenatal or postnatal exposure to PAHs with harmful physiological effects, such as global alteration of DNA methylation in cord blood (Yang et al., 2018), lower birth weight (Lamichhane et al., 2016), smaller head circumference (Al-Saleh et al., 2013) and preterm birth (Cathey et al., 2018), only a limited number of studies have examined the effects of PAH exposure and their impact on the developing fetus during pregnancy. This study determines the urinary hydroxylated PAH metabolites in healthy mothers at delivery, and links maternal urinary levels with neonatal birth outcomes in an e-waste pollution area.

2. Materials and methods

2.1. Study population and sample collection

We performed a cross-sectional study by cluster random sampling method. A total of 257 subjects in the study were recruited from Guiyu (n = 155, an e-waste recycling area) and Haojiang (n = 102, the reference area) during the period of September 2011 to June 2012. These subjects were all healthy pregnant women from the local hospitals in Guiyu and Haojiang with similar socioeconomic status and lifestyles. Informed consent was received from all participants before enrollment and the sample size was dependent on those voluntary participants within that period of sampling time. A questionnaire was completed by each subject for obtaining information on general socioeconomic characteristics, overall health and pregnancy characteristics, residential history and distance from an e-waste recycling area, occupational history and whether jobs were related to e-waste, as well as the drinking and smoking habits of the family members. Mothers, from total of 257 mother/newborn pairs, voluntarily donated their urine before delivery. Neonatal physiological indices of birth weight, head circumference, height and Apgar score were measured by medical professionals after delivery. Maternal urine samples were collected, in a urine collection cup (BD Vacutainer, Plymouth, UK) marked with the subject's identification code, and placed on ice in a portable refrigerator for transport to the analytical laboratory where samples were stored at - 20 °C until analysis. The study protocol was approved by the Human Ethical Committee of Shantou University Medical College, China.

2.2. Chemicals and preparations

Standard reagents of 1-naphthol (1-Nap) (purity 99.8%), 2-naphthol (2-Nap) (purity 99%), and 1-, 2-, 3-, 4-, 9-phenanthrenol (1-, 2-, 3-, 4-, 9-Phe) (purity 99%) were purchased from Dr. Ehrenstorfer (Augsburg, Germany), and 1-OHPyr (purity 98%) was purchased from Aldrich (Milwaukee, WI, USA). HPLC grade methanol and acetonitrile were purchased from Tedia (Tedia, Fairfield, USA). The β-glucuronidase (100,000 Fishman units/mL)/arylsulphatase (800,000 Roy units/ml) enzyme mixture was obtained from Roche Diagnostics GmbH (Penzberg, Germany). HPLC grade acetic acid was purchased from Fisher (Thermo Fisher Scientific, Geel, Belgium). Acetic acid sodium salt was purchased from Acros (New Jersey, USA) and water was obtained from a Milli-Q water purification system (Millipore, Bedford, MA, USA). All glassware was rinsed with methanol before use.

2.3. PAH metabolite extraction and analysis

The PAH metabolite extraction procedure for urinary samples was based on prior methods with minor modifications (Elovaara et al., 2003). In brief, a 5 mL aliquot of urine was adjusted to pH 5.5 with 1 M acetic acid. Then the mixture was buffered with 500 μL 1 M acetate buffer (pH 5.5) containing 20 μL β-glucuronidase/arylsulfatase, and incubated at 37 °C for 16 h. After hydrolysis, the solution was extracted by solid phase extraction (SPE, Supelco) using a Sep-Pak C18 cartridge (500MG/6ML, Agilent). Before use, the C18 cartridge was prewashed with 5 mL methanol and 10 mL water. The sample solution was loaded onto a cartridge, and passed through the sorbent by using a vacuum manifold (Supelco, USA), then washed with 5 mL water and 5 ml 30% methanol. Analytes were eluted with 3 ml 100% methanol, and dried with nitrogen, using a QGT-12 pressure blowing concentrator (Quandao, Shanghai, China) at 40 °C. The residue was redissolved in 500 μL of methanol. Before HPLC analysis, samples were filtered with a Milex Durapore PVDF (13 mm, 0.45 μm pore size) filter.

The external standard method was used for analysis performed by an HPLC system consisting of a Waters 2475 Multi-Wavelength Fluorescence Detector, Waters 600 system controller, Waters 2707 autosampler, a vacuum degasser, column thermostat, and RP C-18 column (symmetry 300, 5 μm (particle size), 4.6*250 mm). The mobile phase (1 ml/min) consisted of acetonitrile (eluent B) and water (eluent A) for a binary gradient: 30% B for 2 min, 30–46% B (2–12 min) and hold (12–16 min), 46–55% B (16–17 min), 55–65% B (17–20 min), 65–70% B (20–23 min) and hold (23–25 min), 70–85% B (25–26 min), back to 30% B (26–27 min) and hold for 27–35 min (30% B). The excitation and emission wavelengths of the fluorescence detector were 227 and 332 nm for 1-, 2-Nap (0–16 min), 256 and 370 nm for 1-, 2-, 3-, 4-, 9-Phe (16–24.5 min), 240 and 387 nm for 1-OHPyr (24.5–35 min), respectively. The injection volume was 20 μL, and column temperature was 40 °C.

2.4. Urinary creatinine assay

Creatinine assay was carried out using the Cayman Chemical Creatinine Assay (Cayman Chemical Company, UK). The assay relies on Jaffe's reaction, wherein a yellow or orange color is formed when the metabolites are treated with alkaline picrate. The color derived from the creatinine is destroyed at acidic pH, so the difference in color intensity measured at OD495 before and after acidification is proportional to the creatinine concentration. A creatinine standard curve was then constructed for urine creatinine concentration determination.

2.5. Quality assurance and quality control (QA/QC)

We conducted instrumental blanks at intervals to guarantee the accuracy of instrument analysis. The method detection limit (MDL) for targeted compounds was 0.5–0.78 ng/mL. For the calibration curve, we made standard work solution containing each standard in methanol and quantitated 1-OH-phe and 9-OH-phe from the calibration curve of 1-OH-phe, 2-OH-phe and 3-OH-phe from the calibration curve of 2-OH-phe. Linearity for a seven-point OHPAH, using the external standard method, was normal ($r^2 > 0.99$). We also performed pre-experiments to ensure target PAH metabolite recovery in urine samples. A known amount of certain standard work solution mixed with certain urinary samples were co-eluted and finally quantified by HPLC. Results for recovery of targeting compounds were 43.32–92.33% and relative standard deviation (RSD) to insure the reproducibility of recovery results ranged (%) from 1.07 to 17.00 (Supplemental Table 1). However, 1-Nap was not stable both in the recovery analysis and measurement in samples due to its extreme low peak response (Supplemental Fig. 1), leading to uncertain results in HPLC, thus 1-Nap data were not shown in this study.

2.6. Statistical analysis

The results are presented as mean ± SD or Median ± S.E. The concentrations of OHPAHs were normalized to creatinine, to correct for the dilution of urine, and expressed as μg/g creatinine. Sample values below the limit of detection (LOD) were assigned a value equal to LOD/2. Comparisons between groups were made by *t*-test or Chi-square test. As PAH metabolite concentrations displayed a skewed distribution, we conducted a Spearman correlation analysis to examine the association between each PAH metabolite in the exposed and reference groups, respectively. Multiple linear regression models were used to evaluate relevant factors contributing to PAH exposure in the exposed and reference groups, respectively. To provide more detailed differences of environmental exposure on neonatal birth outcomes, we stratified our data by PAH metabolite levels in quartiles (the first quartile was designated as low level group, and the fourth quartile as high level group) to demonstrate changes of birth outcome indexes under different PAH metabolite levels. Standardized mean difference (SMD) values within the 95% confidence interval (95%CI) were calculated when compared with each another (i.e., the fourth quartile vs. the first quartile). I-square (I^2) was indicative of the statistical significance elevated for the analyzed groups. An I^2 value below 50% represents good heterogeneity between the comparable groups.

Furthermore, we used quantile regression models to confirm this non-linear association of neonatal birth outcomes with total PAH metabolite levels via adjustment of several confounders including age, family members smoking, maternal education level, and area of residence. In the regression models, we divided the independent variable of total PAH metabolites into four dummy variables in line with quartiles. One dummy variable would be automatically omitted when integrated into the model. So we set the first quartile (Q1) of total PAH metabolite concentrations as the fiducially explained variable to weigh the last three quartiles (Q2, Q3, Q4) in the contribution of birth outcomes. A $p < 0.05$ or 0.01 in a two-tailed test was considered as statistically significant. All data were recorded in a Microsoft Excel database and then input into analyzing software 19.0 SPSS (IBM Inc., USA). Figures were plotted by Stata 12.0 edition (StataCorp LP Inc., USA).

3. Results

3.1. Demographic characteristics

A total of 257 pregnant women were enrolled in the study. There was a mean age of 26.63 y and 27.68 y in the Guiyu exposure group (n = 155) and the Haojiang reference group (n = 102), respectively (Table 1, $p > 0.05$). Women in Guiyu had a lower education level and BMI (prior to pregnancy) ($p < 0.01$), and had a higher consumption of alcohol ($p < 0.05$). No significant difference between the two groups was found for family income, maternal age, maternal smoking and family member smoking. Neonatal birth outcome indices including BMI, head circumference and Apgar 1 score were lower in Guiyu when compared to the Haojiang group ($p < 0.01$). Both birth length and gestational age were both increased in Guiyu, although we observed no significant difference in neonatal weight between the two groups.

3.2. PAH metabolite concentrations

All PAH metabolites were adjusted to creatinine and expressed as μg/g creatinine (Table 2). The total median concentration of maternal urinary PAH metabolites in Guiyu was 6.87 μg/g creatinine with P_{25} to P_{75} ranging from 4.35 to 10.24 μg/g creatinine, higher than the 3.90 μg/g creatinine, with P_{25} to P_{75} ranging from 2.79 to 6.19 μg/g creatinine ($p < 0.01$), for Haojiang. We computed the sum of 2+3-OHPhe and 1+9-OHPhe in place of the individual compounds, as we found the concentrations of these individual metabolites to be low and difficult to separate from other metabolite peaks during analysis, based on pre-experiments. All PAH metabolites in Guiyu were higher than those in Haojiang ($p < 0.01$). 2-OHNap was the dominant metabolite, followed by 1-OHPyr, 1+9-OHPhe, 2+3OHPhe and 4-OHPhe. Both have the same order of predominance. The concentration of the ΣOHPhe was lower than for 2-OHNap. We then compared each PAH metabolite concentration, following normalization to creatinine (μmol/mol creatinine) (Supplemental Table 2). A similar pattern and trend were found for PAH metabolite concentrations consistent with a unit in μg/g creatinine. We used Spearman correlation analysis to examine the relationship between each PAH metabolite in the exposed and reference groups, respectively (Table 3). We found all metabolites were more closely related to each other in exposed group than those in the reference group, and showing a likelihood of a common derivation.

3.3. Factors related to PAH metabolite levels

Multiple linear regression analysis was used to estimate factors correlating with the logarithm of the 2-OHNap concentration in the exposed and reference groups collectively (Table 4) and separately (Supplemental Table 3 and Supplemental Table 4). We found that recycling in homes contributed the most to 2-OHNap concentration ($\beta = 0.144$; 95% CI: 0.023, 0.366, Table 4). Both the exposed and reference groups showed that family member smoke was positively associated with 2-OHNap, and family income level was negative

Table 1
Characteristics of the study subjects in Guiyu and Haojiang groups.

Characteristics	Guiyu (n = 155)		Haojiang (n = 102)		χ^2	t	*p*
	N	Mean ± SD	N	Mean ± SD			
Maternal education level					34.056		<0.001
Primary school	43		17				
Junior high school	99		51				
Senior high school	7		13				
University	0		14				
Family income (RMB)							
≤30,000	93		69		5.259		0.385
30,000–60,000	23		18				
60,000–90,000	21		9				
90,000–120,000	7		1				
120,000–150,000	5		3				
≥150,000	6		2				
Maternal age, years	145	26.63 ± 4.319	100	27.68 ± 4.259		- 1.873	0.062
Maternal smoker	2		0		4.358		0.113
Family member smoker	91		52		2.300		0.317
Maternal alcohol consumption	5		0		6.340		0.042
Maternal BMI, kg/m^2	141	17.50 ± 6.598	91	20.48 ± 3.384		- 3.979	<0.001
Neonatal gender					0.539		0.463
Male	87		52				
Female	65		47				
Neonatal weight, g	154	3236.36 ± 439.71	99	3225.25 ± 449.85		0.194	0.846
Neonatal height, cm	154	51.77 ± 2.265	99	50.24 ± 1.079		6.276	<0.001
Neonatal BMI, kg/m^2	154	11.96 ± 1.605	98	12.68 ± 1.363		- 3.693	<0.001
Neonatal head circumference, cm	153	34.06 ± 2.139	101	35.42 ± 2.030		- 5.055	<0.001
Apgar 1 score	155	9.51 ± 1.053	102	9.86 ± 1.062		- 2.620	0.009
Gestational age, weeks	142	39.89 ± 0.826	99	39.16 ± 1.883		4.068	<0.001

Table 2
PAH metabolite concentrations in maternal urine from Guiyu and Haojiang (μg/g creatinine).

PAH metabolites (creatinine-adjusted)	Guiyu (n = 155)		Haojiang (n = 102)		*p*
	Median ± S.E	Interqartile range (25th - 75th)	Median ± S.E	Interqartile range (25th −75th)	
2-OHNap	3.71 ± 0.618	2.131–6.036	2.41 ± 0.703	1.730 ± 4.317	0.006
2+3-OHPhe[a]	0.31 ± 0.071	0.151–0.523	0.17 ± 0.042	0.093 ± 0.312	<0.001
1+9-OHPhe[b]	0.54 ± 0.080	0.333–0.910	0.34 ± 0.110	0.166 ± 0.578	<0.001
4-OHPhe	0.22 ± 0.126	0.088–0.477	0.09 ± 0.051	0.035 ± 0.260	0.006
1-OHPyr	1.19 ± 0.217	0.643–2.207	0.57 ± 0.141	0.285 ± 1.267	<0.001
ΣOHPhe[c]	1.20 ± 0.182	0.816–2.037	0.63 ± 0.181	0.391 ± 1.129	<0.001
ΣOHPAHs	6.87 ± 0.804	4.350–10.236	3.90 ± 0.919	2.785 ± 6.188	<0.001

[a] 2+3-OHPhe is the sum of 2-OHPhe and 3-OHPhe.
[b] 1+9-OHPhe is the sum of 1-OHPhe and 9-OHPhe.
[c] ΣOHPhe is the total of 2+3-OHPhe, 1+9-OHPhe and 4-OHPhe.

Table 3
Spearman correlation analysis between each PAH metabolite in urine.

	2-OHNap	2+3-OHPhe	1+9-OHPhe	4-OHPhe	1-OHPyr	ΣOHPhe	ΣPAHs
2-OHNap	**1**	0.374**	0.209#	0.248*	0.109	0.376**	0.882**
2+3-OHPhe	0.462**	**1**	0.376**	0.429**	0.429**	0.710**	0.554**
1+9-OHPhe	0.455**	0.481**	**1**	0.314**	0.316**	0.817**	0.395**
4-OHPhe	0.304**	0.436**	0.404**	**1**	0.430**	0.620**	0.442**
1-OHPyr	0.406**	0.411**	0.522**	0.455**	**1**	0.425**	0.450**
ΣOHPhe	0.470**	0.416**	0.822**	0.725**	0.549**	**1**	0.618**
ΣPAHs	0.848**	0.542**	0.653**	0.514**	0.680**	0.730**	**1**

The upper right part of the table is based on data coming from reference group (Haojiang).
The lower left part of the table is based on data coming from exposed group (Guiyu).
0.05 < p value < 0.10.
* Significant at 0.05 level (2-tailed).
** Significant at 0.01 level (2-tailed).

associated with 2-OHNap, but not statistically significant (Supplemental Table 3 and Supplemental Table 4). In addition, multiple linear regression analysis was also used to estimate factors correlating with the logarithm of the 1-OHPyr concentration in the exposed and reference groups collectively (Supplemental Table 5) and respectively (Supplemental Table 6 and Supplemental Table 7). Residence in Guiyu was significantly correlated with elevated 1-OHPyr ($\beta = 0.069$; 95% CI: 0.053, 0.326) in Supplemental Table 5. Although the adjusted regression equation had significance, no significance was observed for other factors, including maternal education, family member smoking and distance of residence from an e-waste recycling shop. No significant factors for 1-OHPyr were

Table 4
Multiple linear regression analysis of the log 2-OHNap concentration and exposure source-related factors.

Relevant factors	Logarithm of 2-OHNap (n = 257)						
	B[a]	β[b]	95% Confidence Interval for B	R^2	Adjusted R^2	F	*p*
				0.043	0.024	2.265	0.049
Maternal education level	- 0.025	- 0.055	(- 0.081, 0.030)				
Recycling in house	0.179	0.144	(0.023, 0.366)				
Residence in Guiyu	0.031	0.046	(- 0.060, 0.123)				
Family member smokes	0.092	0.109	(- 0.012, 0.196)				
Residence distance from e-waste recycling workshop	−0.010	−0.035	(- 0.046, 0.026)				

[a] B: unstandardized coefficients.
[b] β: standardized coefficients.

found in the exposed and reference groups, respectively (Supplemental Table 6 and Supplemental Table 7).

3.4. Association of PAH metabolites with neonatal birth outcomes

A detailed difference in neonatal birth outcomes under different PAH metabolite levels was investigated using the standardized mean difference (SMD). The comparison between high PAH metabolite levels (the fourth quartile) and low exposure (the first quartile) was shown (Fig. 1). In general, high PAH metabolite levels showed reduced effects on neonatal birth outcomes (overall SMD = −0.09; 95% CI: −0.15, −0.03), and the I^2 values were all less than 25%. Compared to low levels of PAH metabolites, we found reduced head circumference (subtotal SMD = −0.24; 95% CI: −0.37, −0.11), BMI (subtotal SMD = −0.16; 95% CI: −0.29, −0.03) and Apgar 1 score (subtotal SMD = −0.17; 95% CI: −0.30, −0.04), and increased birth length (subtotal SMD = 0.25; 95% CI: 0.11, 0.38). No significance was found for birth weight. Specially, high levels of 1+9-OHPhe (SMD = −0.39; 95% CI: −0.74, −0.03) and the ΣOHPAHs (SMD = −0.36; 95% CI: −0.71, −0.00) produced reduced head circumference. Individually, 1-OHPyr (SMD = −0.47; 95% CI: −0.82, −0.11) showed a decrease to BMI, and both 4-OHPhe (SMD = −0.39; 95% CI: −0.74, −0.04) and 1-OHPyr (SMD = −0.54; 95% CI: −0.90, −0.19) reduced Apgar 1 score. We also compared medium exposure (second and third quartile), only to find that medium levels in the third quartile exhibited an increase for birth length (subtotal SMD = 0.14; 95%CI: 0.01, 0.27), but no other significant effects were observed under medium levels (Supplemental Fig. 2).

Further, we performed quantile regression models to examine this non-linear association of total PAH metabolites with neonatal birth outcomes after adjusting for confounding factors (Fig. 2). After adjusting for confounders, such as maternal age, education, maternal smoking, neonatal gender, family member smoking, gestational age and maternal BMI, significant decreases were found in Q3 and Q4 for birth weight, equal to a decrease of 218.90 g (95% CI: −437.24, −0.57) and 234.56 g (95% CI: −452.00, −17.13) in weight per interquartile increase in ΣOHPAHs. A loss of 1.72 (95% CI: −2.96, −0.48) and 1.14 cm (95% CI: −2.25, −0.04) in head circumference before and after adjustment were associated with Q4, respectively. Apgar 1 score were inversely correlated with Q3 both before (−0.46; 95% CI: −0.68, −0.24) and after adjustment (−0.42; 95% CI: −0.66, −0.18), whereas BMI was decreased in Q3 (−1.11; 95% CI: −1.87, −0.35) and Q4 (−1.06; 95% CI: −1.82, −0.31) after adjustment. Birth length showed a negative trend but no significance.

4. Discussion

PAHs are ubiquitously environmental toxicants worldwide and are prone to be metabolized into hydroxyl compounds. In this study, we determined the concentrations of hydroxylated PAH metabolites in maternal urine and assessed their associations with neonatal birth outcomes. We find that total and individual urinary PAH metabolites in a polluted e-waste area are higher than those in a non-polluted area, but that both groups have similar exposure profiles and trends for all PAH metabolites, especially for exposure to 2-OHNap and 1-OHPyr, suggesting that residents in e-waste-polluted areas are exposed to higher concentrations of PAHs. Recent studies have detected urinary PAH metabolites as the main biological matrix for PAH burden in both human and animals (Lotz et al., 2016; Bortey-Sam et al., 2017). The level trend of reported metabolites in the general population is comparatively consistent, but for developing countries, such as Vietnam, Korea and China, the human burden is usually higher than in European countries and the United States (Bartolome et al., 2015; Thai et al., 2015; Lin et al., 2016). Even in these developing countries, the PAH exposure differs as is found in a previous large-scale epidemiological study that the total concentrations of OHPAHs, found in the seven Asian countries, are in the following increasing order: Malaysia < Japan < China < India < Vietnam < Korea < Kuwait (Guo et al., 2013). However, Concentrations of total PAH metabolites in maternal urine from the e-waste area, reported in this survey, are the highest compared with studies investigated in Poland (Polanska et al., 2014a,b), Israel and the United States (St et al., 2012; Levine et al., 2015), which should be concerned in the future.

PAH metabolite levels are usually higher in people from e-waste polluted areas, but sometimes lower than occupational exposure. A similar study from our recycled electronic garbage town in southern China demonstrates that the mean value of 1-OHPyr in local residents (1.1 μmol/mol creatinine) is slightly higher than those reported for iron foundry workers, automobile repair workers, and firefighters, and the mean value of 2-OHNap (11.3 μmol/mol creatinine) is much higher than that of shipyard and aircraft maintenance workers, but much lower than some occupational exposures, as well two-fold higher than that in our prior study (5.6 μmol/mol creatinine) (Wang et al., 2014). However, our results are consistent with prior data that 2-OHNap and 1-OHPyr are the predominant individual PAH metabolites. In contrast, another investigation from Guangzhou, China, reporting on kindergarten-age children, showed that urinary OHPAH levels are 2–30 times higher than those of American children 6–11 years of age, and in their study the median concentration of 2-OHNap (4.1 μg/g creatinine) is lower than that in our study, but the total OHNap concentrations are higher, and the total OHPhe (3.4 μg/g creatinine) is two-fold higher, compared with our results (Li et al., 2015). The extremely high levels of OHPAHs in their study may be attributable to the amounts of detected metabolites and the length of time for exposure. Furthermore, the comparative PAH metabolite levels from multiple studies vary and are discrepant, possibly due to the amount of PAH metabolites and individual PAH metabolic rates (Grova et al., 2017), as suggested by a recent study showing that two

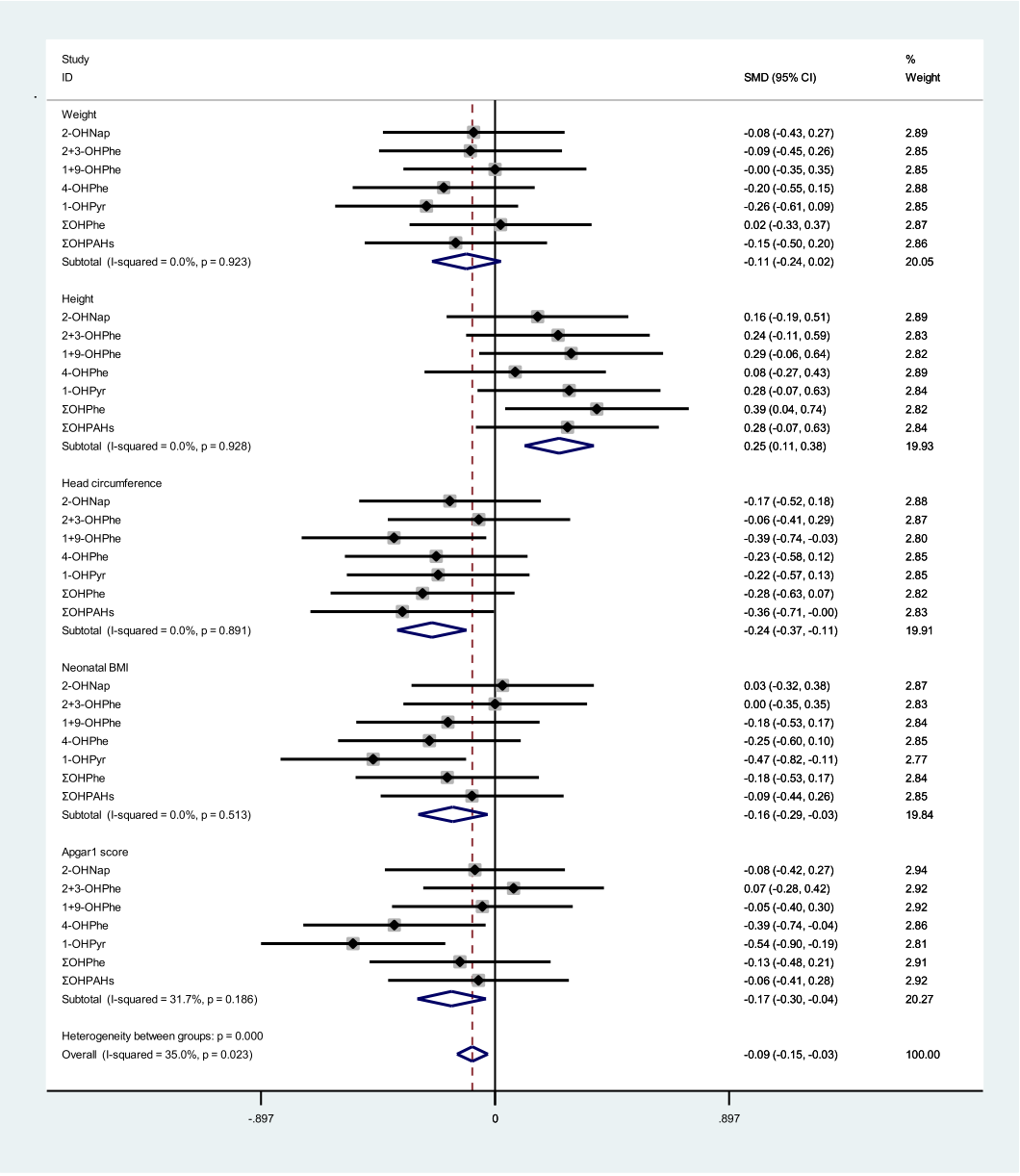

Fig. 1. Differences in birth outcome size under high PAH metabolite levels in the fourth quartile compared with low levels in the first quartile, as indicated by the standardized mean difference (SMD) values. Note: a line or a quadrangular box, free of crossover with the longitudinal axis, represents a statistical significance in the 95% CI.

urinary PAH metabolites, 1-OHPyr and 2-OHNap, can decrease monthly, in clean-up workers from an oil spill area (Noh et al., 2015).

We then analyzed the risk factors probably related to the elevated PAH metabolites. In the present study, we find that the elevated 2-OHNap concentration is positively associated with e-waste recycling activities in the home, and the 1-OHPyr concentration positively correlates with residence in Guiyu, which is similar to a prior study in Ghana finding that, in e-waste workers, 1-OHPyr is in the highest concentration among five determined congeners (Feldt et al., 2014). This indicates that e-waste recycling could be an important source for specific PAH exposure and human internal PAH metabolite levels, since e-waste recycling via primitive and irregular techniques has resulted in persistent organic toxicants, including PAHs, being released into the surrounding environment, leading to elevated PAH levels in soil and plants, as well as human umbilical cord blood (Alabi et al., 2012; Xu et al., 2013). In reality, PAH exposure sources are varied and complex. In addition to the e-waste source, other common sources may collectively contribute to exposure. Studies have identified that ambient airborne contamination, such as environmental tobacco smoke (Hoh et al., 2012), vehicle emissions and biomass burning emissions (Li et al., 2018), residential heating or wood for cook during daily activities (Singh et al., 2016), the use of a fireplace in the home (Shen et al., 2015), as well as food chain contamination (Paris et al., 2018), can persistently add to personal exposure, sometimes at high levels. Therefore, e-waste and additional daily exposure can largely increase the opportunity and risk of human exposure to PAHs. Here, we highlight e-waste exposure in this study, which will be of particular concern in the future.

Studies have shown that some PAHs can generate morphological changes, inflammatory responses (Ovrevik et al., 2013), oxidative

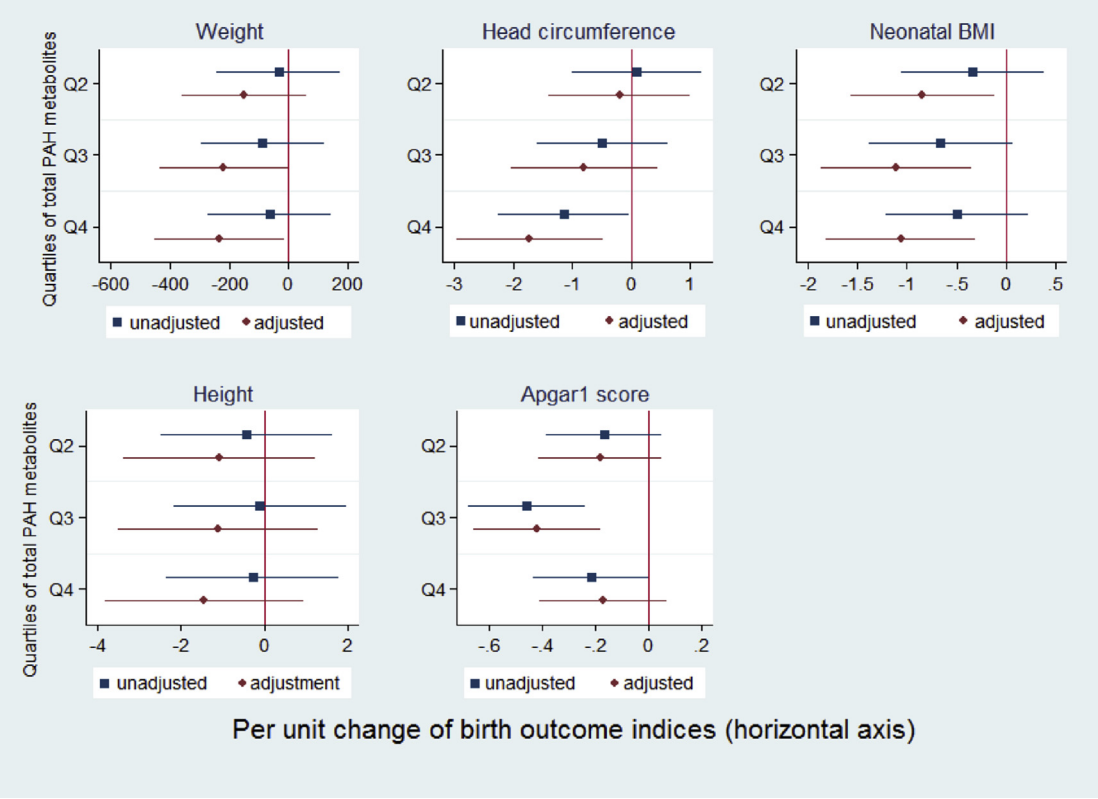

Fig. 2. Quantile regression models for birth outcomes, equal to a unit change in birth outcome per interquartile increase in ΣOHPAHs. The vertical axis represents the quartiles of total PAH metabolite concentrations: Q2 (the second quartile), Q3 (the third quartile), Q4 (the fourth quartile), and the regression coefficient of each quartile was compared with the first quartile when fitted into the model. The green squares and the red circles represent the regression coefficient β values. The short line represents the β range within the 95% confidence interval. A significance of $p < 0.05$ or 0.01 is indicated if the line does not cross the central vertical axis (0). Confounders were adjusted in models such as maternal age, education, maternal smoking, neonatal gender, family member smoking and gestational age. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

stress (Lu et al., 2016), reproductive toxicity (Jeng et al., 2013), neurotoxicity (Perera et al., 2018) and considerable carcinogenic potential (Liao et al., 2011), causing adverse effects on human health. Epidemiological evidence has also indicated that urinary PAH metabolites are associated with undesirable health consequences, including impairment of cognitive dysfunction (Jedrychowski et al., 2015), increased DNA damage (Bai et al., 2016), and differential cardiovascular disease risk (Feng et al., 2014). In the present study, we provide evidence for the association of high PAH metabolite levels (in the fourth quartile) with physiologically reduced neonatal birth outcomes. To identify detailed differences of birth outcomes under different levels of PAH metabolites, we conducted SMD analyses by stratifying data in quartiles. ΣOHPAHs in the fourth quartile present reduced effects on neonatal head circumference, BMI and Apgar 1 score. All metabolites show a trend for negative risk for body weight and, except for ΣOHPhe, display a positive trend for birth length, although neither trend is statistically significant. Again, quantile regression models indicate that ΣOHPAHs in the fourth quartile were inversely associated with certain decreases in body weight, head circumference and BMI, after adjusting for confounding factors. A similar negative association in the third quartile is found for body weight, BMI and Apgar 1 score. No statistical significance is observed in birth length. Previous cross-sectional and longitudinal studies have reported that early exposure to PAHs may influence pregnancy outcomes, including intrauterine growth retardation (Choi et al., 2006), a heightened risk of preterm delivery and a deficit in birth weight (Jedrychowski et al., 2017). To date, few studies have been done to link PAH metabolites with neonatal birth outcomes. Polanska et al. demonstrated that a weak significance exists for the association of neonatal cephalization with ΣOHPhe only after adjusting for potential confounders, which might be explained by the lower concentrations of PAH exposure (Polanska et al., 2014a,b). However, Suzuki et al. found that 1-OHP does not affect birth outcomes at the exposure level in their study subjects (Suzuki et al., 2010). Their results at low exposure levels are consistent with our data in quantile regression models, that low exposure below the median values (i.e. the first and second quartile of PAH metabolite concentrations) exerts no significant influence on birth outcomes. However, PAH metabolites are associated with physiological decreases in birth outcomes at our monitoring levels. Therefore, our current data of the associations between PAH metabolites and birth outcomes in this study demonstrate that high levels of PAH metabolites in e-waste-polluted areas may be risk factors for adverse birth outcomes. Further studies should be implemented to confirm this finding and focus on the health risks of PAH exposure.

Finally, it should be noted that e-waste produces a complex mixture of individual toxic pollutants, including many heavy metals and other organic chemicals, which may jointly or antagonistically trigger adverse effects to birth outcomes. In this study, we only detect one type of PAH contaminants. Although the reduced effect on birth outcomes might result from other chemicals, for instance, our previous finding of an association of placental or umbilical cord blood PBDE exposure with birth outcomes (Wu et al., 2010; Xu et al., 2014), especially for head circumference, the present study continues to observe an inverse association of high PAH

metabolite levels with birth outcomes, showing that PAHs can be a possible effective indicator for potential health effects under certain concentrations such as in the fourth quartile of this study. Moreover, the lack of the chronological order was also an important factor to accurately evaluate the association between PAH exposure and birth outcomes because the half-life of PAHs taken in by humans ranges from several to dozens of hours. We could only make a short-term evaluation of PAH exposure during the past day or several days due to the difficulty in sampling at different window of pregnancy, and preliminarily associate the due levels in urinary OHPAHs with neonatal birth outcomes. Long-term exposure of PAH exposure in e-waste areas and health effects may be paid attention in future studies.

5. Conclusions

In total, in this typical e-waste area, we find PAH metabolites in maternal urine at high levels than those reported for some European countries and the United States. 2-OHNap and 1-OHPyr are the dominant compounds. A physiologically reduced size in head circumference, BMI and Apgar 1 score are observed in high PAH metabolite levels compared with low levels of OHPAHs, and quantile regression models further indicate that the fourth quartile of ΣOHPAHs are associated with different degree of decreases in birth weight, head circumference and BMI, and the third quartile for Apgar 1 score, after adjusting for confounders. These results suggest that early exposure to high PAH may bring about potential health risks for neonates. Therefore, continuous monitoring to assess prenatal or postnatal health outcomes, is needed in highly polluted areas.

Conflicts of interest

All authors have no competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2018.10.098.

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