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ORIGINAL PAPER

A Targeted Lipidomic Reveals CYP450-Derived Oxylipin Linked to the Inflammatory Response by Polycyclic Aromatic Hydrocarbon Exposure in Children

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Abstract

Polycyclic aromatic hydrocarbon (PAH) exposure is a cause of chronic inflammation. The effect of PAHs on bioactive lipid mediators involved in the inflammatory process remains largely unknown. This study measured ten urinary monohydroxy-PAHs (OH-PAHs), 54 plasma oxylipins, and inflammation-related markers. Children with high PAH exposure had higher levels of ten OH-PAHs, (±)18-HETE, 19(S)-HETE, 5,6-DiHETrE, 9,10-DiHOME, more monocytes, interleukin (IL)-10, tumor necrosis factor (TNF)-α and IL-6 than those with low PAH exposure (all $p < 0.05$). The ΣOH-PAHs were inversely correlated to the levels of anti-inflammatory oxylipins, including 5,6-EET (p for trend = 0.007), 11,12-EET (p for trend = 0.035), 14,15-EET (p for trend = 0.022), and 16(17)-EpDPE (p for trend = 0.043), but positively associated with pro-inflammatory 9,10-DiHOME (p for trend < 0.001). Mediation analyses indicated that cytochrome P450 (CYP)-derived 9,10-DiHOME mediated a separate 42.7%, 31.1%, 57.8%, and 38.5% of the associations between OH-PAHs and monocytes, IL-6, IL-10, TNF-α ($p = 0.017$, 0.014, 0.005 and 0.012, respectively). Our study suggests that CYP-derived oxylipins can be considered sensitive lipid mediators to signal the early inflammation response to PAH exposure.

Keywords Inflammation · Monocyte · Cytokine · PAHs · Metabolomic · PUFAs

Introduction

Polycyclic aromatic hydrocarbons (PAHs) are relatively hydrophobic and stable in the environment due to their aromatic rings and semi-volatility (Gao et al. 2018). A significant PAH source is the incomplete combustion of organic material, such as wood, gas, coal, petroleum, tobacco, and garbage (Mastral et al. 2000; Abdel-Shafy et al. 2016; Alegbeleye et al. 2017). Incomplete combustion of organic plastics during electronic-waste (e-waste) dismantling is considered a significant PAH source in e-waste recycling areas (Xu et al. 2015; Chen et al. 2019). PAHs entering the body can be metabolized by members of the cytochrome P450 (CYP) family into monohydroxy-PAH (OH-PAH) isomers, which have been related to the onset of metabolic syndrome, infertility, inflammation, cancer, cardiovascular disease, and type 2 diabetes (Brocato et al. 2014; Dai et al. 2019; Wang et al. 2012; Yang et al. 2017, 2019, 2020; Yu et al. 2021). Additionally, PAHs perturb lipid metabolism and participate in the early activation of glycerophospholipids, the substrates of phospholipase A2 (PLA2), leading to a downstream

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inflammatory response (Siegrist et al. 2019; Zhang et al. 2017; Wang et al. 2015). Nevertheless, the effect of PAHs on bioactive lipid mediators involved in the inflammatory process remains largely unknown.

Oxylipins are bioactive lipid mediators biosynthesized by non-enzymatic and enzymatic oxidation of ω-6 polyunsaturated fatty acids (PUFAs), including arachidonic acid (AA) and linoleic acid (LA), or ω-3 PUFAs, including α-linolenic acid (α-LA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) (Dennis and Norris 2015; Gabbs et al. 2015; Quehenberger et al. 2010). When cells are in contact with external stimuli, PUFAs are released from membrane-bound phospholipids by activation of PLA2 and subsequent oxidation by three major enzymatic pathways, comprised of CYP epoxygenases/hydroxylases, lipoxygenase (LOX), and cyclooxygenase (COX), to generate oxylipins such as epoxyeicosatrienoic acids (EETs), hydroxyeicosatetraenoic acids (HETEs), leukotrienes (LT), and prostaglandins (PG) (Zivkovic et al. 2011). AA-derived oxylipins are more involved in the pro-inflammatory process, while DHA and EPA-derived oxylipins play a dual role in anti-inflammatory and pro-resolution activities (Serhan et al. 2008; Dennis and Norris, 2015; Divanovic et al. 2013). LA-derived dihydroxy-12Z-octadecenoic acid (DiHOME) species are generally considered pro-inflammatory and cytotoxic, whereas EETs are anti-inflammatory (Gilroy et al. 2016; Zimmer et al. 2018). The complicated signal network of oxylipins regulates various homeostatic and inflammatory processes associated with multiple diseases, such as breast cancer, IgA nephropathy, chronic obstructive pulmonary disease, endometriosis, and cardiovascular disease (Zivkovic et al. 2012; Lee et al. 2016; Nayeem et al. 2018; van der Does et al. 2019; Chocholouskova et al. 2019). Considering that CYP also metabolizes PAHs after entering the human body, it is plausible that oxylipins may participate in the inflammatory response caused by PAH exposure.

Some epidemiological studies found that air pollution is related to the disorder of oxylipins derived from CYP, LOX, and COX pathways and indicates that oxylipins play a vital role in the inflammatory response to environmental exposures in the respiratory system (Martens et al. 2017; Mu et al. 2019; Wang et al. 2021; Yan et al. 2019). However, the link between PAH exposure and oxylipins from different metabolic pathways in preschool children remains unknown. Our previous studies have clarified the impact of PAH exposure on inflammation in preschool children from the perspectives of platelets, cytokines, and immune cells (Zheng et al. 2019; Dai et al. 2019; Cheng et al. 2020). To date, evidence of alterations of bioactive lipid mediators linked to inflammatory response after PAH exposure is lacking. Hence, the primary purposes of this study are: (1) to explore the difference in plasma oxylipin profiles between low and high PAH exposed children; (2) to estimate the association between urinary PAHs and oxylipin signaling pathways; (3) to assess the mediation effect of oxylipins on PAH exposure and inflammatory response.

Materials and Methods

Study Participants and Sample Collection

From November to December 2017, 217 healthy children aged 3- to 6-year-old who were not under medication were enrolled in the study, of which 107 were from Haojiang and 110 were from Guiyu. Guiyu, an e-waste recycling town in southeast China, has a high risk of exposure to contaminants (Huo et al. 2007). Haojiang was regarded as the reference area due to its lack of e-waste pollution. Our studies over the years have found that children in Guiyu have a higher risk of PAH exposure and their urinary PAH levels are always higher than those in Haojiang (Zheng et al. 2019; Dai et al. 2019; Cheng et al. 2020). We selected 100 children from all recruited participants, of which 50 children from Guiyu were regarded as high PAH exposure group, and the other half of children from Haojiang were considered a low PAH exposure group. The child's guardians filled out a survey questionnaire covering their basic information and their family and written informed consent. The study was approved by the Ethics Committee of Shantou University Medical College. All children participated in the physical examination and contributed two fasting blood samples in tubes containing EDTA-K^2 and one-morning spot urine sample. Peripheral blood samples were analyzed for immune cell counting; urine samples were stored in a freezer at − 20 °C until PAH metabolite measurement; serum and plasma samples were stored at − 80 °C until cytokines and oxylipins measurement.

Urinary PAH Metabolite Analysis

Ten OH-PAHs measured in this study are 1-hydroxypyrene (1-OHPyr), 1-hydroxyphenanthrene (1-OHPhe), 1-hydroxynaphthalene (1-OHNap), 2-hydroxyphenanthrene (2-OHPhe), 2-hydroxynaphthalene (2-OHNap), 2-hydroxyfluorene (2-OHFlu), 4-hydroxyphenanthrene (4-OHPhe), 3-hydroxyphenanthrene (3-OHPhe), 9-hydroxyfluorene (9-OHFlu), and 9-hydroxyphenanthrene (9-OHPhe). They were analyzed using a gas chromatograph-mass spectrometer (7890A-5975C, Agilent Technologies Inc., USA) in the same method as previous studies (Huo et al. 2019; Cheng et al. 2020). The internal standards were 1-OHPyr-d9 and 1-OHNap-d7. The relative standard deviation percentage of multiple tests of quality control samples was 3.2–16.8%, and each kind of OH-PAH recovery was 73–119%. The regression coefficient (R^2) for each standard curve exceeded 0.995.

Urinary creatinine concentrations were measured using a Cayman Chemical Creatinine Assay (Cayman Chemical, UK). The levels of ten PAH metabolites were calculated using standard curves from the same batch. The urinary OH-PAH concentrations were expressed as μg/mmol creatinine.

Plasma Oxylipin Profiling Analysis

Oxylipin extraction is described in detail in the Supporting Information. An ultra-high performance liquid chromatography (UPLC) Shim-pack UFLC SHIMADZU CBM30A system (Kyoto, Japan) coupled to tandem mass spectrometry (MS/MS) (Applied Biosystems SCIEX QTRAP 6500PLUS, Framingham, USA) was used for the analysis of plasma oxylipins. An ACQUITY UPLC HSS T3 column (1.8 μm 2.1 × 100 mm) was maintained at 40 °C, and the injection volume was ten μL. Chromatographic separation was carried out at a constant flow rate of 0.4 mL/min. The mobile phase consisted of (A) acetonitrile/water/acetic acid (60/40/0.002, v/v/v) and (B) acetonitrile/isopropanol (50/50, v/v). The following gradient conditions were: 0–4.0 min, 0.1–55% B; 4.0–5.0 min, 55–99% B; 5.0–6.8 min, 99% B; 6.8–7.0 min, 99.0–0.1% B; 7.0–10.0 min, stop. Oxylipins were determined in negative electrospray ion mode. Nebulizer gas, curtain gas, and turbo-gas were set at 40 psi, 35 psi, and 40 psi, respectively. Turbo ion spray source temperature was 550 °C. All extracted samples were prepared as a composite sample regarded as the quality control sample. A quality control sample was run every ten stitches during the analytical process to ensure repeatability. Scheduled multiple reaction monitoring modes analyzed oxylipins to eliminate the interference of non-target ions. Figure S1 shows that the quantification and repeatability are excellent. According to peak type information and retention time, the peak identification, manual integration, and signal-to-noise calculations were performed using MultiQuant™ software. All standard curves showed good linearity for all analytes, with R^2 values above 0.99 (Table S1). Recovery rates of the internal standards were 58.1–112.3%. The limits of detection (LOD) are provided (Table S2). The peak area of oxylipin below the LOD was assigned to LOD/2 for subsequent statistical analysis. Overlapping analysis of total ion chromatography of a quality control sample was used to ensure the repeatability of oxylipin extraction and detection (Fig. S2).

Monocyte and Cytokine Measurements

According to standard procedures, an automatic blood analyzer (XT-1800i, Sysmex Corporation, Japan) was used for monocyte counting within 8 h of sample collection. Serum interleukin (IL)-10, IL-6, and tumor necrosis factor (TNF)-α were determined with the ProcartaPlex Human Cytokine Panel (eBioscience, USA).

Statistical Analysis

The Kolmogorov–Smirnov normality test analyzed the distribution of the numerical data. Student's *t* test and Mann–Whitney *U* test were performed to examine statistical differences for normal and skew continuous variables. Results were expressed as mean ± SD and median, respectively. A chi-square test was performed to determine the distribution difference of categorical variables.

The PAH metabolites and oxylipins concentrations were log10-transformed to approximate a normal distribution before multivariate analysis. First, unsupervised principal component analysis (PCA) was used to evaluate the quality control samples. Next, supervised orthogonal partial least square-discriminant analysis (OPLS-DA) separated the oxylipin profiles of the PAH high and low exposure groups. The contribution of each oxylipin to the overall separation of the two groups was quantified in the OPLS-DA model by the variable importance in the projection score (VIP). Then, the 999-time permutation test was used to examine the overfitting of the model (Triba et al. 2015). *p* values of oxylipin data were corrected for multiple testing by the false discovery rate (FDR) of Benjamini-Hochberg. Oxylipins with a VIP score > 1.0 and FDR < 0.05 were considered as significant differential metabolites.

We investigated the associations between PAH exposure and oxylipins using multivariate linear regressions. The concentration of urinary ΣOH-PAHs is trisected among all children ($n = 100$). The 1st tertile was regarded as the reference variable to weigh the 2nd and 3rd tertiles. Mediation analysis was used to assess the potential value of oxylipins in the relationship between PAH exposure and inflammatory response. We also performed a series of sensitivity analyses for pathways with significant associations with PAH exposure: models that were not adjusted for family member smoking; models that only adjusted for gender, age, and BMI; and models stratified by gender.

The results were analyzed using GraphPad Prism version 7.0 (GraphPad, CA), SPSS version 24.0 (IBM Corporation, USA), R programming language version 4.0.3 (R Foundation for Statistical Computing), and SIMC version 14.0 (Umetrics AB, Sweden). $p < 0.05$ under the two-tailed test was considered a significant difference.

Results

Demographic Characteristics of the Participants

The baseline information of 100 children is summarized in Table 1. The children's gender, age, BMI, urinary creatinine, and monthly household income were not different between the low and high PAH exposed group (all

Table 1 Characteristics of the participants

Characteristics	Low PAH exposed group ($n=50$)	High PAH exposed group ($n=50$)	Statistics	p^a
Gender [*n* (%)]			$\chi^2=0.000$	1.000
Male	25 (50.0)	25 (50.0)		
Female	25 (50.0)	25 (50.0)		
Age (years, mean ± SD)	4.94 ± 0.81	4.95 ± 0.82	$t=$-0.063	0.950
BMI (kg/m^2, mean ± SD)	15.20 ± 1.30	15.11 ± 1.22	$t=0.356$	0.723
Urinary creatinine (mg/dL, median, P25, P75)	31.52 (15.89, 58.39)	31.64 (21.24, 56.96)	$Z=-1.013$	0.311
Family member smoking [cigarettes, *n* (%)]			$\chi^2=15.936$	0.003
Non-smoking	26 (52.0)	12 (24.0)		
< 2	7 (14.0)	2 (4.0)		
2–10	4 (8.0)	12 (24.0)		
11–20	10 (20.0)	15 (30.0)		
> 20	3 (6.0)	9 (18.0)		
Monthly household income [yuan, *n* (%)]			$\chi^2=7.951$	0.093
< 1500	1 (2.0)	3 (6.0)		
1500–3000	5 (10.0)	9 (18.0)		
3000–4500	6 (12.0)	12 (24.0)		
4500–6000	9 (18.0)	10 (20.0)		
> 6000	29 (58.0)	16 (32.0)		
Paternal education levels [*n* (%)]			$\chi^2=44.481$	< 0.001
Primary school	0 (0.0)	7 (14.0)		
Middle school	10 (20.0)	35 (70.0)		
Vocational school	9 (18.0)	3 (6.0)		
High school	6 (12.0)	3 (6.0)		
College/University	25 (50.0)	2 (4.0)		
Maternal education levels [*n* (%)]			$\chi^2=29.925$	< 0.001
Primary school	1 (2.0)	10 (20.0)		
Middle school	11 (22.0)	28 (56.0)		
Vocational school	6 (12.0)	3 (6.0)		
High school	7 (14.0)	4 (8.0)		
College/University	25(25.0)	5 (10.0)		

SD standard deviation, *BMI* body mass index

[a]Normal continuous variables were compared using the Student's *t* test; non-normal continuous variables were compared using the Mann–Whitney *U* test; categorical variables were compared using the chi-square test

$p > 0.05$). Family member smoking and parental education levels differed between the two groups (all $p < 0.05$).

Concentrations of Urinary PAH Metabolites

The urinary concentrations of all OH-PAHs in 100 children are shown in Table 2. Compared with the low PAH exposed group, the median levels of urinary OH-PAHs ranged from 1.92- (for 9-OHFlu) to 3.9-fold (for 1-OHPhe) higher in the high PAH exposed group (all $p < 0.01$). In both groups of children, the order of contributions of urinary PAH metabolites was ΣOHPhe > ΣOHFlu > ΣOHNap.

Profiles of Plasma Oxylipins and Differential Metabolites

Out of 54 measured oxylipins, 17 metabolites had > 20% values below the LOD and were eliminated from further statistical analysis (Table S2). Thirty-seven kinds of oxylipin biosynthetic pathways as shown in Fig. S3. Table S3 shows the median concentrations (nM) of 37 kinds of plasma oxylipins for the low and high PAH exposed groups. The plasma oxylipin profiles of the low and high PAH exposed groups are presented in Fig. 1A. The scoring plot from unsupervised PCA indicated the close clustering of quality control samples (Fig. 1B), indicating that the analysis process

Table 2 Comparison of urinary PAH metabolite concentrations (μg/mmol creatinine) in participants

Metabolites	Low PAH exposed group ($n=50$)				High PAH exposed group ($n=50$)				p^a
	Percentile			Contribution (%)	Percentile			Contribution (%)	
	25th	50th	75th		25th	50th	75th		
1-OHNap	0.18	0.45	1.16	10.2	0.45	1.13	2.39	10.7	0.001
2-OHNap	0.18	0.45	1.00	10.9	0.51	1.15	2.56	9.2	0.001
2-OHFlu	0.19	0.45	0.98	11.7	0.55	1.41	2.61	11.0	< 0.001
9-OHFlu	0.13	0.52	1.34	12.7	0.67	1.00	2.13	9.9	0.001
1-OHPhe	0.12	0.36	0.79	9.2	0.36	1.41	2.69	11.5	< 0.001
2-OHPhe	0.09	0.21	0.77	6.5	0.17	0.59	1.92	7.2	0.001
3-OHPhe	0.21	0.43	0.98	12.6	0.53	1.51	2.67	10.6	< 0.001
4-OHPhe	0.10	0.39	1.07	9.9	0.66	1.18	2.46	11.0	< 0.001
9-OHPhe	0.13	0.22	0.66	7.6	0.50	1.23	2.41	10.5	< 0.001
1-OHPyr	0.28	0.53	0.79	8.8	0.46	1.04	2.41	8.4	0.001
ΣOHNap	0.39	1.14	2.04	21.1	1.10	2.61	5.11	19.9	< 0.001
ΣOHFlu	0.42	1.10	2.22	24.4	1.41	2.75	5.13	20.9	< 0.001
ΣOHPhe	0.87	1.90	3.99	45.7	3.19	6.59	12.35	50.8	< 0.001
ΣOH-PAHs	2.69	5.16	8.45	100.0	7.55	15.30	25.75	100.0	< 0.001

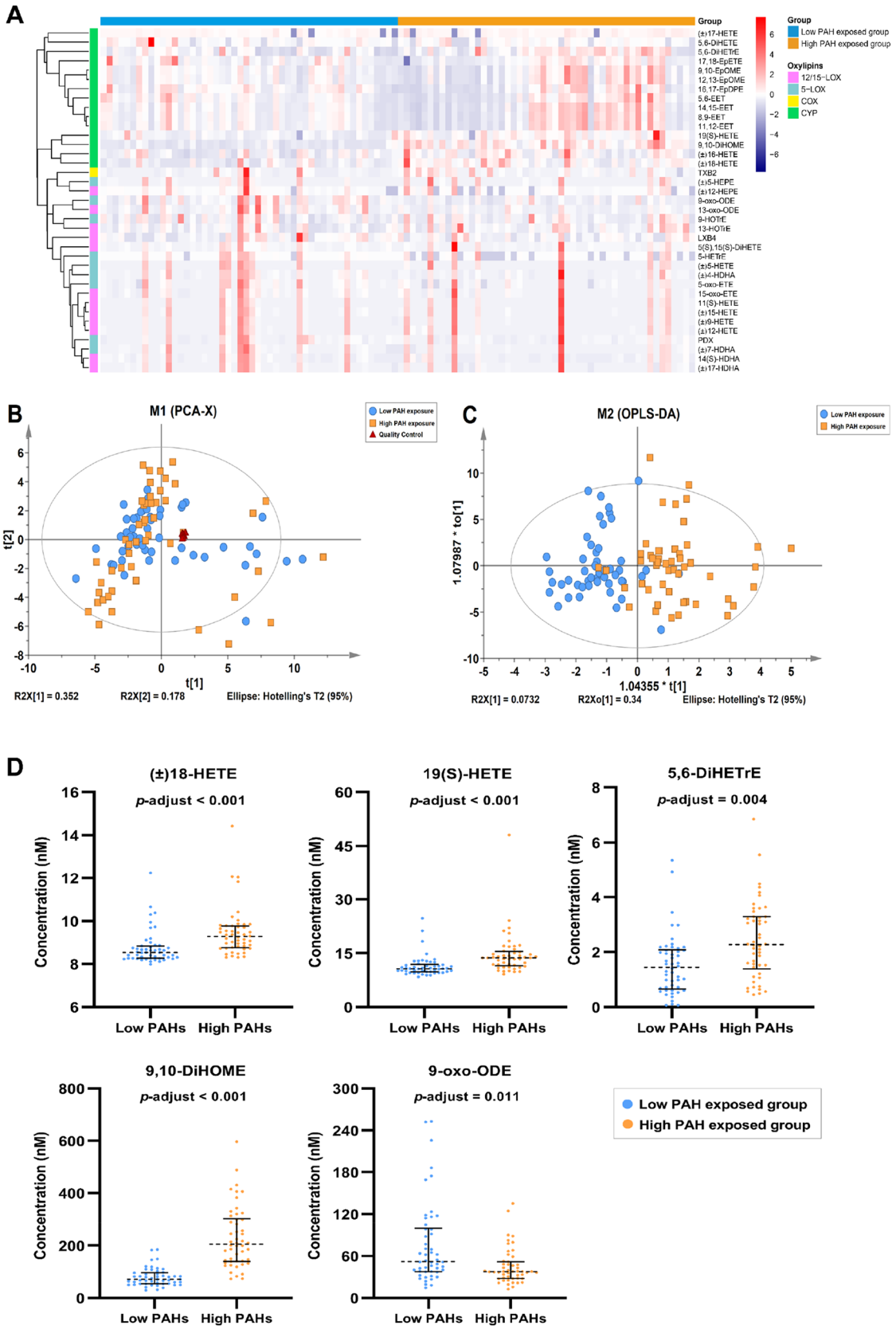
PAH, polycyclic aromatic hydrocarbon; 1-OHNap, 1-hydroxynaphthalene; 2-OHNap, 2-hydroxynaphthalene; 2-OHFlu, 2-hydroxyfluorene; 9-OHFlu, 9-hydroxyfluorene; 1-OHPhe, 1-hydroxyphenanthrene; 2-OHPhe, 2-hydroxyphenanthrene; 3-OHPhe, 3-hydroxyphenanthrene; 4-OHPhe, 4-hydroxyphenanthrene; 9-OHPhe, 9-hydroxyphenanthrene; 1-OHPyr, 1-hydroxypyrene; ΣOHNap, the sum of 1-OHNap and 2-OHNap; ΣOHFlu, the sum of 2-OHFlu and 9-OHFlu; ΣOHPhe, the sum of 1-OHPhe, 2-OHPhe, 3-OHPhe, 4-OHPhe, and 9-OHPhe; ΣOH-PAHs, the sum of urinary monohydroxylated PAH metabolite concentrations

[a]Non-normal continuous variables were compared using the Mann–Whitney *U* test

is highly repeatable. The scoring plot of the supervised OPLS-DA (Fig. 1C) displayed a clear separation of plasma oxylipins between the two groups. The Q^2 was negative in the 999-time permutation test, suggesting that the OPLS-DA model was not overfitting (Fig. S4). Compared with the low PAH exposed group, we identified five oxylipins were elevated in the high PAH exposed group among which (±)18-HETE (median: 9.27 nM vs. 8.54 nM, p-adjust < 0.001, VIP = 2.39), 19(S)-HETE (median: 13.69 nM vs. 10.68 nM, p adjust < 0.001, VIP = 1.01), 5,6-dihydroxyeicosatrienoic acid (DiHETrE) (median: 2.27 nM vs. 1.45 nM, p adjust < 0.01, VIP = 1.32), and 9,10-DiHOME (median: 204.80 nM vs. 70.9 nM, p adjust < 0.001, VIP = 3.27). However, 9-oxo-10(E),12(Z)-octadecadienoic acid (9-oxo-ODE) (median: 37.70 nM vs. 52.23 nM, p adjust < 0.05, VIP = 1.25) was lower in the high PAH exposed children than in the low PAH exposed children (Fig. 1D).

Correlation Between Urinary PAH Metabolites and Plasma Oxylipins

We found that nine oxylipins were associated with the ΣOH-PAHs when they were categorized as tertiles (p values for trends were all < 0.05) (Fig. 2). In the unadjusted model, compared with the 1st tertile, the ΣOH-PAHs in the 3rd tertile was positively associated with CYP-derived (±)18-HETE, and negatively associated with 5-LOX derived (±)4-hydroxy-docosahexaenoic acid (HDHA) and (±)7-HDHA, and 12/15-LOX derived (±)12-hydroxyeicosapentaenoic acid (HEPE). In the adjusted model (corrected for BMI, gender, age, parental education levels, monthly household income and family member smoking), compared with the 1st tertile, the ΣOH-PAHs in the 2nd and 3rd tertiles were negatively associated with CYP-derived 5,6-EET [B with 95%CI − 0.189 (− 0.314, − 0.064) for 2nd tertile; − 0.229 (− 0.357, − 0.100) for 3rd tertile], 11,12-EET [− 0.126 (− 0.246, − 0.007) for 2nd tertile; − 0.136 (− 0.258, − 0.014) for 3rd tertile], and 14,15-EET [− 0.166 (− 0.311, − 0.022) for 2nd tertile; − 0.178 (− 0.326, − 0.030) for 3rd tertile]. The concentration of ΣOH-PAHs in the 3rd tertile was negatively associated with CYP-derived 16(17)-epoxydocosapentaenoic acid (EpDPE) [B with 95%CI − 0.186 (− 0.330, − 0.043)], but positively associated with CYP-derived 9,10-DiHOME [B with 95%CI 0.066 (0.013, 0.129)]. In the sensitivity analyses, the relationships between the ΣOH-PAHs and CYP-derived oxylipins were not materially changed in models that were not adjusted for family member smoking. Still, some differences in models were adjusted only for gender, age, and BMI and in models stratified by child gender (Table S4). Therefore, we consider adjusting monthly


A
Group
(±)17-HETE
5,6-DiHETE
5,6-DiHETrE
17,18-EpETE
9,10-EpOME
12,13-EpOME
16,17-EpDPE
5,6-EET
14,15-EET
8,9-EET
11,12-EET
19(S)-HETE
9,10-DiHOME
(±)16-HETE
(±)18-HETE
TXB2
(±)5-HEPE
(±)12-HEPE
9-oxo-ODE
13-oxo-ODE
9-HOTrE
13-HOTrE
LXB4
5(S),15(S)-DiHETE
5-HETrE
(±)5-HETE
(±)4-HDHA
5-oxo-ETE
15-oxo-ETE
11(S)-HETE
(±)15-HETE
(±)9-HETE
(±)12-HETE
PDX
(±)7-HDHA
14(S)-HDHA
(±)17-HDHA
Group
Low PAH exposed group
High PAH exposed group
Oxylipins
12/15−LOX
5−LOX
COX
CYP
B
M1 (PCA-X)
Low PAH exposure
High PAH exposure
Quality Control
t[2]
t[1]
R2X[1] = 0.352
R2X[2] = 0.178
Ellipse: Hotelling's T2 (95%)
C
M2 (OPLS-DA)
Low PAH exposure
High PAH exposure
1.07987 * to[1]
1.04355 * t[1]
R2X[1] = 0.0732
R2Xo[1] = 0.34
Ellipse: Hotelling's T2 (95%)
D
(±)18-HETE
p-adjust < 0.001
19(S)-HETE
p-adjust < 0.001
5,6-DiHETrE
p-adjust = 0.004
9,10-DiHOME
p-adjust < 0.001
9-oxo-ODE
p-adjust = 0.011
Concentration (nM)
Low PAHs
High PAHs
Low PAH exposed group
High PAH exposed group

◂**Fig. 1** Comparison of plasma oxylipin profile between low and high PAH exposed groups. **A** Heatmap of plasma oxylipins between low and high PAH exposed groups. *LOX* lipoxygenase, *COX* cyclooxygenase, *CYP* cytochrome P450. **B** Scoring plots of the unsupervised PCA model. *PCA* principal component analysis. **C** Scoring plots of the supervised OPLS-DA model. *OPLS-DA* orthogonal partial least squares discrimination analysis. **D** Scatter dot plots of the most significantly changed oxylipins in plasma of children. *p* adjusted indicates the multiple testing adjusted *p* values using the Benjamini–Hochberg procedure. The dotted and solid lines represent the median and P25 or P75, respectively

household income and parental education levels in the regression model.

Inflammation-Related Markers

Compared to the low PAH exposed children, the mean counts of monocytes ($0.56 \pm 0.2 \times 10^9$/L, $p < 0.001$) and median concentrations of TNF-α (6.51 pg/mL, $p < 0.001$), IL-6 (6.96 pg/mL, $p < 0.001$), and IL-10 (1.51 pg/mL, $p < 0.001$) were significantly higher in the high PAH exposed children (Fig. 3).

Mediation Analysis

We built a statistical model to assess the mediation effect of changes in plasma 9,10-DiHOME on the inflammatory response of PAH exposure (Fig. 4). We found that 9,10-DiHOME mediated a separate 42.7%, 31.1%, 57.8%, and 38.5% of the association between ΣOH-PAHs and monocytes, IL-6, IL-10, and TNF-α ($p = 0.017$, 0.014, 0.005 and 0.012, respectively).

Discussion

To our knowledge, we firstly reported the associations between PAH exposure and changes in a wide range of oxylipins in children. We compared 37 oxylipins from the CYP, COX, and LOX pathways between low and high PAH exposed groups. We observed that a higher urinary ΣOH-PAH level was related to more pro-inflammatory oxylipins and associated with less anti-inflammatory oxylipins in children. Mediation analysis revealed that CYP-derived 9,10-DiHOME had a significant mediating effect in the association of urinary ΣOH-PAH with the inflammatory response. These findings indicate that the alterations of oxylipins may predate the immune response, and CYP-derived oxylipins can be regarded as sensitive lipid mediators to reveal the early inflammatory response to PAH exposure.

Oxylipins are a group of lipid metabolites generated via oxygenation of PUFA and participate in the balance of anti- and pro-inflammatory responses in the body (Dominguez-Perles et al. 2019; Serhan et al. 2008). Here, we found that high PAH exposed children have elevated levels of four oxylipins targeted by the CYP pathway, three from AA [(±)18-HETE, 19(S)-HETE, 5,6-DiHETrE], and one from LA (9,10-DiHOME), but have lower levels of 9-oxo-ODE, which originates from LA and results from 5-LOX pathway metabolism. CYP-derived epoxyeicosatrienoic acids (EETs) reduced the recruitment of pro-inflammatory monocytes during peripheral zymosan-induced inflammation, thereby reducing inflammatory pain (Gilroy et al. 2016). However, EETs are highly unstable in vivo, as 5,6-EET can be metabolized by soluble epoxide hydrolase (sEH) into 5,6-DiHETrE, which plays a pro-inflammatory function (Newman et al. 2005). In addition, CYP-derived 9,10-epoxyoctadecamonoenoic acids (EpOME) also be metabolized into 9,10-DiHOME by sEH, both of which can activate NF-κB and mediate inflammation (Hildreth et al. 2020; Zimmer et al. 2018; Viswanathan et al. 2003). 5-LOX-derived 9-oxoODE is a natural ligand for PPARγ signaling and participates in anti-inflammatory responses by suppressing NF-κB activation (Shiraki et al. 2005). CYP-derived (±)18-HETE plays a role in insulin resistance, and its elevation is related to microvascular insulin resistance (Chadderdon et al. 2016). CYP-derived 19(S)-HETE has a cardioprotective role and contributes to maintaining body fluid and circulatory homeostasis. Its increase has cardiovascular protection (Elkhatali et al. 2015; Kaide et al. 2003; Wang et al. 2004). The higher CYP-derived pro-inflammatory oxylipins and lower 5-LOX-derived anti-inflammatory oxylipins in children with high PAH exposure indicate the imbalance of their immune response. Our previous data showed that children living in a high PAH exposed area are at higher risk of low-grade inflammation and cardiovascular endothelial inflammation (Dai et al. 2019; Zheng et al. 2019). Therefore, these oxylipins derived from different pathways might be considered potential biomarkers for assessing the inflammatory effects of internal exposure.

As we know, PAHs are converted into mutagenic OH-PAH isomers by the CYP family, including CYP1A, CYP1B, CYP2C, and CYP2E (Gao et al. 2018). CYP epoxygenases oxidize AA to EET, DHA to EpDPE, and LA to EpOME (Anne et al. 2011). Thus, the CYP family controls the metabolic activation of PAHs and monitors the synthesis of EETs, EpDPE, and EpOME. Some enzymes, including CYP1A1, CYP1A2, and CYP1B1, contribute to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-mediated increases in oxylipin levels (Hankinson et al. 2016). Siegrist et al. (2019) found that low molecular weight PAHs can induce the activation of glycerophospholipids and the increase of downstream expression of COX2 and eicosanoids in mouse lung epithelial cells. Our results show that elevated urinary ΣOH-PAHs are associated with CYP-derived oxylipins, as

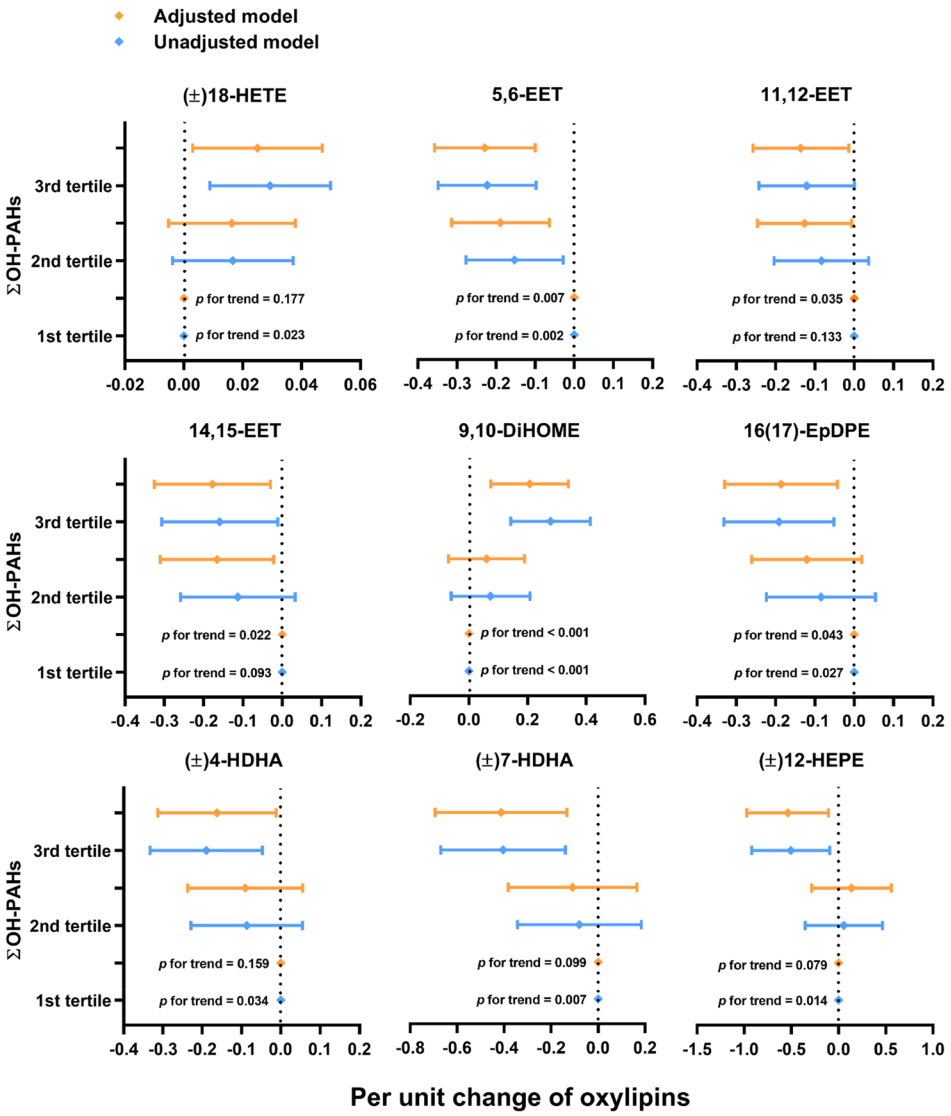


Fig. 2 Association of urinary ΣOH-PAHs with plasma oxylipins in children. All models were adjusted for age, gender, BMI, family member smoking, paternal and maternal education levels, and monthly household income. The 1st tertile was regarded as the reference variable to weigh the 2nd and 3rd tertiles. *ΣOH-PAHs* the sum of urinary monohydroxylated PAH metabolite concentrations

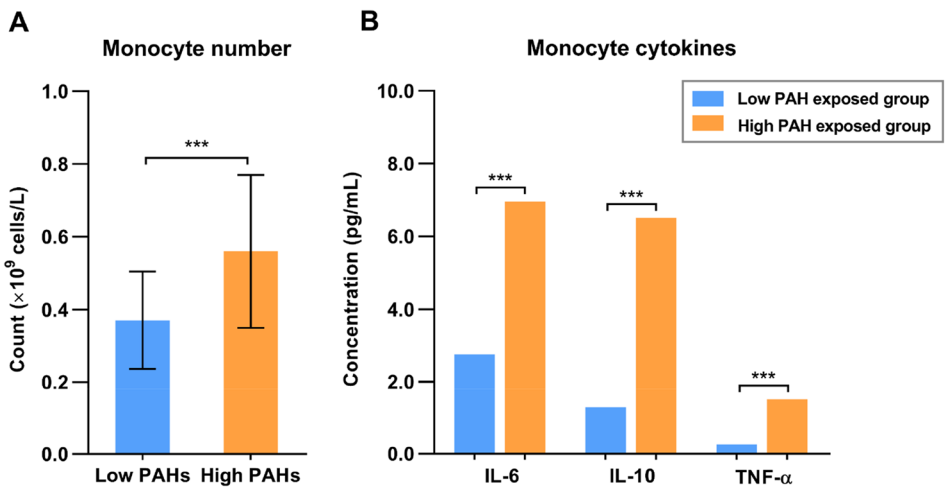


Fig. 3 Comparison of monocyte inflammatory response between the low and high PAH exposed groups. **A** The monocyte count difference between the two groups presents data as means and standard deviation. **B** The difference in monocyte-derived cytokines between the two groups. Data are presented as median. *IL* interleukin, *TNF* tumor necrosis factor. $^{***}p < 0.001$

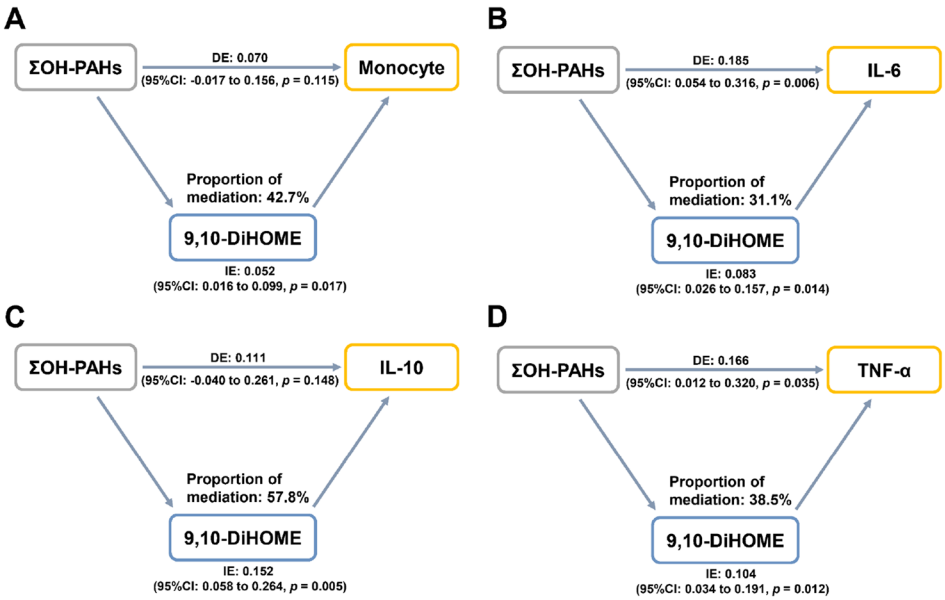


Fig. 4 Estimated proportion of the association between PAH exposure and monocyte inflammatory response mediated by 9,10-DiHOME. The figure presents 9,10-DiHOME levels in plasma as a mediator, the estimate of the indirect effect (IE), the estimation of the direct effect (DE), and the proportion of mediation [(IE/DE + IE) × 100]. Model adjusted for age, gender, BMI, family member smoking, paternal and maternal education levels, and monthly household income; 5000 bootstrap samples

demonstrated by the increase in pro-inflammatory oxylipin (9,10-DiHOME) and decreased anti-inflammatory oxylipins (16,17-EpDPE, 11,12-EET, 14,15-EET, and 5,6-EET). These findings suggest CYP-derived oxylipins may be new biomarkers for evaluating the inflammatory effects of PAH exposure, which provides a unique perspective to elucidating the toxic impact of PAH on inflammation. Similar to our results, Aung et al. (2021) found that PAH metabolites significantly correlated to CYP450 products, including 9(S)-HODE, 5,6-EET, and 14(15)-EET in pregnant women. Not all CYP-derived oxylipins [e.g., 5,6-DiHETrE, (±)18-HETE, 19(S)-HETE] with differences between high and low PAH exposed groups were significantly correlated with urinary ΣOH-PAHs, which may be because these differences are not directly caused by PAH exposure. At the same time, in pregnant women, Welch et al. (2021) observed that other chemical contaminants such as organophosphate ester and phthalate metabolites were associated with higher levels of CYP-derived pro-inflammatory DiHOMEs. There was no significant association between CYP-derived 5,6-DiHETrE and ΣOH-PAHs, but its upstream metabolite 5,6-EET was significantly associated with PAH exposure. Other population studies observed that exposure to air pollution is linked to alterations of 5-LOX, 12/15-LOX, and COX-derived oxylipins in newborns and pregnant women (Mu et al. 2019; Yan et al. 2019). Wang et al. (2021) observed that exposure to the particulate matter might activate the formation of CYP-derived 5,6-DHET, characterized by airway inflammation. Although we could not confirm their results, this may be because our study was focused mainly on the toxicity of PAHs metabolized by the CYP family. In contrast, the toxicity components of air pollution and biodiesel exhaust are more complex. Thus, different pollutants have other toxic effects on the biosynthetic pathway of oxylipins, and the specific interactions between toxicants and oxylipins deserve further study.

Our previous study has shown that PAH exposure is associated with a cytokine storm characterized by altered concentrations of multiple anti- and pro-inflammatory cytokines in children with high PAH exposure (Cheng et al. 2020). We also observed that children from the high PAH exposed group have higher counts of monocyte and concentrations of TNF-α, IL-10, and IL-6 than those from the low PAH exposed group. Monocytes are an essential part of innate and adaptive immunity and actively participate in and coordinate the inflammatory response with the cytokines mentioned above (Abdulkhaleq et al. 2018). Bioactive lipid mediators can be classified as pro- or anti-inflammatory oxylipins, which can induce the production of anti-or pro-inflammatory cytokines (e.g., TNF-α, IL-10, IL-1β, and IL-6) (Ávila-Román et al. 2018; Bosviel et al. 2017; Pauls et al. 2018; Li et al. 2020). CYP-derived EETs can reduce the recruitment of pro-inflammatory monocytes and promote the pro-resolution phenotype in the monocyte lineage (Gilroy et al. 2016). CYP-derived 9,10-DiHOME has adverse effects on apoptosis, vasodilation, increased cellular oxidative stress, mitochondrial dysfunction, and suppression of neutrophil respiratory burst activity (Thompson et al. 2007; Viswanathan et al. 2003).

Furthermore, we found that CYP-derived 9,10-DiHOME was different between the two groups and significantly correlated with urinary ΣOH-PAHs. The mediation analysis could provide clues for further study of the potential function of CYP-derived 9,10-DiHOME between PAH exposure and monocyte and related cytokines. Results showed that plasma 9,10-DiHOME

plays a mediator between PAH exposure and monocyte, anti-inflammatory cytokine IL-10, and pro-inflammatory cytokines TNF-α and IL-6. Similar to our study, Shen et al. (2018) found that blood levels of 9,10-DiHOME and 12,13-DiHOME were elevated after exposure to welding fumes in adults, which may be related to systemic inflammatory responses. In addition, So et al. (2021) found that plasma specialized lipid mediators metabolized by EPA and DHA have a significant effect on ex vivo monocyte inflammatory response by regulating different cytokine expressions, such as monocyte chemoattractant protein-1, TNF-α, IL-10, and IL-6, suggesting that these oxylipins have immunomodulatory activities. Additional studies are needed to elucidate better the potential mediating role of CYP-derived oxylipins in the immune response caused by PAH exposure.

Our study firstly examines the impact of PAH exposure on CYP, COX, and LOX-derived oxylipin profiles in children and provides epidemiological evidence for the mediating role of CYP-derived 9,10-DiHOME in the effect of PAH exposure on monocytes and related pro-and anti-inflammatory cytokines. Nevertheless, some limitations should be acknowledged that may limit our data interpretation. First, single spot urinary and blood samples were used to measure PAH metabolites and oxylipin profiles, which may be random and thus may lead to attenuation estimates. Further repeated analysis of urinary OH-PAHs is needed to improve the measurement accuracy. Second, the power of association analysis may be limited by the small sample size of this study. We followed up with children aged 3–7 in the same area every year to ensure the relative stability of the study population and continue to advance based on previous findings. Third, this cross-sectional study cannot explain causality, limiting the power of mediation analysis. However, our interpretation of the results is based on the biological mechanism reported in previous experimental studies. Additionally, we corrected to the greatest extent possible confounding factors, including BMI, gender, age, monthly household income, maternal and parental education levels, and family member smoking. Still, we cannot avoid the possibility that other confounding factors were not included in our study.

Conclusions

We report for the first time the association between PAH exposure and oxylipins reflecting the CYP pathways in children, which is mainly manifested as an increase in pro-inflammatory oxylipins and a decrease in anti-inflammatory oxylipins. We may provide a new perspective on PAHs and chronic inflammation. CYP-derived 9,10-DiHOME might significantly mediate the association between PAH exposure and inflammatory response. Thus, CYP-derived oxylipins are potent lipid mediators for assessing the inflammatory effects of PAH exposure.

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Data Availability The datasets used in the current study are available from the corresponding authors on reasonable request.

Declarations

Competing Interests The authors have no relevant financial or non-financial interest to disclose.

Ethical Approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Shantou University Medical College (SUMC-2015-19).

Consent to Participate The participant's guardians written informed consent.

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