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Elevated biomarkers of sympatho-adrenomedullary activity linked to e-waste air pollutant exposure in preschool children

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ABSTRACT

Air pollution is a risk factor for cardiovascular disease (CVD), and cardiovascular regulatory changes in childhood contribute to the development and progression of cardiovascular events at older ages. The aim of the study was to investigate the effect of air pollutant exposure on the child sympatho-adrenomedullary (SAM) system, which plays a vital role in regulating and controlling the cardiovascular system. Two plasma biomarkers (plasma epinephrine and norepinephrine) of SAM activity and heart rate were measured in preschool children (n = 228) living in Guiyu, and native (n = 104) and non-native children (n = 91) living in a reference area (Haojiang) for > 1 year. Air pollution data, over the 4-months before the health examination, was also collected. Environmental $PM_{2.5}$, PM_{10}, SO_2, NO_2 and CO, plasma norepinephrine and heart rate of the e-waste recycling area were significantly higher than for the non-e-waste recycling area. However, there was no difference in plasma norepinephrine and heart rate between native children living in the non-e-waste recycling area and non-native children living in the non-e-waste recycling area. $PM_{2.5}$, PM_{10}, SO_2 and NO_2 data, over the 30-day and the 4-month average of pollution before the health examination, showed a positive association with plasma norepinephrine level. $PM_{2.5}$, PM_{10}, SO_2, NO_2 and CO concentrations, over the 24 h of the day of the health examination, the 3 previous 24-hour periods before the health examination, and the 24 h after the health examination, were related to increase in heart rate. At the same time, plasma norepinephrine and heart rate on children in the high air pollution level group (≤ 50-m radius of family-run workshops) were higher than those in the low air pollution level group. Our results suggest that air pollution exposure in e-waste recycling areas could result in an increase in heart rate and plasma norepinephrine, implying e-waste air pollutant exposure impairs the SAM system in children.

1. Introduction

Air pollution is an important global environmental problem and associated with many health burdens in many parts of the world. It is estimated that the vast majority of global population (89%) lives in unhealthy levels of outdoor air pollution exceeding World health Organization (WHO) air quality standards [fine particulate matter ($PM_{2.5}$) annual mean of 10 μg/m^3] (Brauer et al., 2012; WHO, 2016). A growing body of evidence linking outdoor air pollution with morbidity and mortality of cardiovascular and respiratory disease, cancer and all-cause has been found (Cao et al., 2011; Kan et al., 2008; Wang et al., 2018; Zhang et al., 2013). The health effects of outdoor air pollution will further escalate in the future, approximately 3.3 million premature deaths per year is attributed to outdoor air pollution in both cities and rural areas in 2010, increasing to about 6.6 million in 2050 (Lelieveld et al., 2015).

With the rapid development of technology and science and increases in consumer needs, the requisite continual improvement and updating of electronic equipment has resulted in the accumulation of electronic waste (e-waste), including the end-of-life electrical and electronic products for homes and offices, and even large electrical equipment, such as telecommunication equipment and medical equipment (Chen

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et al., 2011; Grant et al., 2013; Zhang et al., 2017). It is estimated that global ewaste will be 65.4 million tons by 2017 (Breivik et al., 2014; Baldé et al., 2014). However, its poor management is an important environmental health problem (Chen et al., 2011). Based on the Basel Convention regulations, the flow of hazardous materials across national borders is prohibited (LaDou and Lovegrove, 2008; Lundgren, 2012). In 2006, the Nairobi Declaration on the Environmentally Sound Management of Electrical and Electronic Waste was adopted by the Basel Convention's eighth meeting of COP and launched on a global scale (Lundgren, 2012). In addition, in order to better manage e-wastes, a series of tools have also been designed and developed, including Extended Producer Responsibility, Material Flow Analysis, Multi-Criteria Analysis and Life Cycle Assessment (Kiddee et al., 2013). Unfortunately, approximately 70% of the world's e-waste is still deposited and processed in China every year (Robinson, 2009; Chen et al., 2011; Hicks et al., 2005; LaDou and Lovegrove, 2008). Recent studies revealed that the lion's share of global e-waste still be received in China, and some scarce mineral resources are acquired from e-waste to continue economic and social development (Dai et al., 2017; Bakhiyi et al., 2018). E-waste contains many toxic organic pollutants and metals, and the informal recycling and dismantling processes can lead to air pollution and the release of toxicants into the environment, especially in developing countries (Huo et al., 2007; Liu et al., 2008; Lu et al., 2016; Wang et al., 2016; Wu et al., 2012; Xu, L. et al., 2015b).

Emission of air pollutants from e-waste recycling and dismantling activities in China is known. Studies indicate that combustion of e-waste can cause the emission of air pollution. For example, the process of coal burning for the melting of circuit boards will release pollutants into the atmosphere; moreover, some processes used within the informal e-waste recycling and dismantling sectors, including grinding and melting, also release dust, fumes and smoke into the air (Dai et al., 2017; Huo et al., 2007; Zeng et al., 2016; Zhang et al., 2017; Zheng et al., 2016). Guiyu, a town in Shantou, Guangdong Province, China, is one of the largest e-waste recycling and dismantling locations in the world, and has a > 30-year history of e-waste recycling and dismantling (Huo et al., 2007; Lundgren, 2012), and air pollution has become prevalent as a result of informal e-waste recycling and dismantling activity. Previous studies show that the geometric mean concentration of $PM_{2.5}$ (49.9 μg/m^3) in Guiyu is higher than the reference group (37.6 μg/m^3), and PM air samples of Guiyu contain potentially carcinogenic and highly toxic pollutants such as Pb (geometric mean: 160 μg/m^3), Cd (geometric mean: 5.7 μg/m^3), Cr (geometric mean: 4.5 μg/m^3), Mn (geometric mean: 17 μg/m^3), PBDEs (mean ± SD: 16575 ± 13,286 pg/m^3), PCDD/F (64.9–2365 pg/m^3) and PBDD/Fs (8.124–61 pg/m^3) (Li et al., 2007; Deng et al., 2007; Zeng et al., 2016; Zheng et al., 2016). Air pollutants of e-waste dismantling areas have raised public concern in recent years (Zheng et al., 2016; Zeng et al., 2016). At the same time, the risks for developing cardiovascular disease (CVD) and cancer are significantly elevated in e-waste recycling and dismantling workers and people living in e-waste recycling areas (Lu et al., 2017; Lu et al., 2016; Guo et al., 2013; Wang et al., 2012).

Although an increasing number of studies show that air pollution is a risk factor for CVD, the mechanisms by which air pollution leads to CVD is not fully understood (Brook et al., 2010; Dehbi et al., 2017; Zhang et al., 2014; Mustafic et al., 2012; Day et al., 2017). Assessment of sympatho-adrenomedullary (SAM) function in humans is one of the major fields in cardiovascular disease research (Grassi and Esler, 1999; Grassi et al., 2015; Guyenet, 2006; Malpas, 2010). Prior studies show that plasma epinephrine and norepinephrine and heart rate are reliable biomarkers of assessment of SAM activity (Chang et al., 1991; Esler et al., 1985; Kawada et al., 2006; Miyamoto et al., 2003; Peronnet et al., 1982; van den Meiracker et al., 1989). Generally, the SAM system transduces biological information either primarily through adrenergic receptors to regulate and control cardiovascular system, such as β1-adrenergic receptors, α1-adrenergic receptors and β2-adrenergic receptors (Masuo et al., 2005; Osei-Owusu and Scrogin, 2004; Rohrer et al., 1998). In mammals, epinephrine and norepinephrine are the signaling hormones of the SAM system (Roy and Rai, 2008). In addition, among the numerous cardiovascular physiology parameters, heart rate is also an independent risk factor for CVD and a key vital sign to assess the physiological status in the clinical settings (Cooney et al., 2010; Fleming et al., 2011; Palatini, 2007).

To date, toxicological studies have shown that although the SAM system is not typically viewed as a primary target of numerous pollutants, pollutants can cause SAM dysfunction (Geraldes et al., 2016). The mechanisms underlying pollutant-induced SAM dysfunction could involve some central mechanisms and pathways, such as impairment of cholinergic and dopaminergic transmission and environmental pollutant-induced oxidative stress (Bielarczyk et al., 1996; Bourjeily and Suszkiw, 1997; Brockel and Cory-Slechta, 1999). A previous study showed that pollutant exposure can promote the autonomic nervous system dysfunction and increase chemoreceptor sensitivity in rats (Geraldes et al., 2016). Either short-term or long-term exposure to cigarette smoke, in either active or passive smoking, affects the balance of the autonomic nervous system, leading to predominance of sympathetic nervous activity (Middlekauff et al., 2014). A recent study shows that long-term $PM_{2.5}$ exposure increases blood pressure in rats, abnormal sympathetic nervous system activation and inflammation of the hypothalamus play an important role in this process (Ying et al., 2014). There have been no epidemiological studies concerning SAM dysfunction of preschool children by ambient air pollutant exposure. However, it is clear that the relationship between air pollution and exposure to some chemical contaminants and impaired nervous system development of children is closely related. Interaction of air pollution and heavy metals with the nervous system can lead to nervous system dysfunction and alter the balance of neurotransmitters, and some pollutant-induced neurobehavioral disorders can continue through youth (Annavarapu and Kathi, 2016; Geraldes et al., 2016; Kioumourtzoglou et al., 2016; Needleman, 1990; Valciukas et al., 1978). At the same time, it is worth noting that cardiovascular regulatory changes in childhood could contribute to the development and progression of cardiovascular events at older ages (Feinstein and Quivers, 1997). Therefore, we predict that the SAM system in children living in e-waste recycling areas may be affected as a result of air pollutant exposure.

The aim of this study is to investigate changes in the SAM system of children living in an e-waste recycling area, and explore the effect of air pollutant exposure on the SAM system by measuring plasma epinephrine and norepinephrine, and heart rate in children as a function of air pollutant data in a typical e-waste recycling area. We hope to provide a scientific basis for further study concerning the effect of air pollutant exposure on development of the child cardiovascular system.

2. Materials and methods

2.1. Sample collection

423 of the 591 children (3- to 6-years of age) from two different kindergartens in Guiyu and Haojiang, from November to December 2016, were recruited and had blood samples taken (Fig. 1). The response rate was 71.6% (Guiyu: 67.5%/Haojiang: 77.1%). Guiyu and Haojiang are both small rural towns in Shantou. There are many similarities between Haojiang (the non-e-waste recycling area) and Guiyu (the e-waste recycling area) in population, cultural background, living habits, climate conditions socioeconomic status, but there is no e-waste pollution in Haojiang (Zhang et al., 2017). For the purpose of this study, non-native children are defined as children who were not born in Shantou, and neither of their parents was a native of Shantou. All participants and guardians of children consented to participate, and signed informed consent. This study was also approved by the Human Ethics Committee of Shantou University Medical College, China. Self-administered questionnaire surveys were completed by each participant (or guardian), covering their personal information about age, gender,

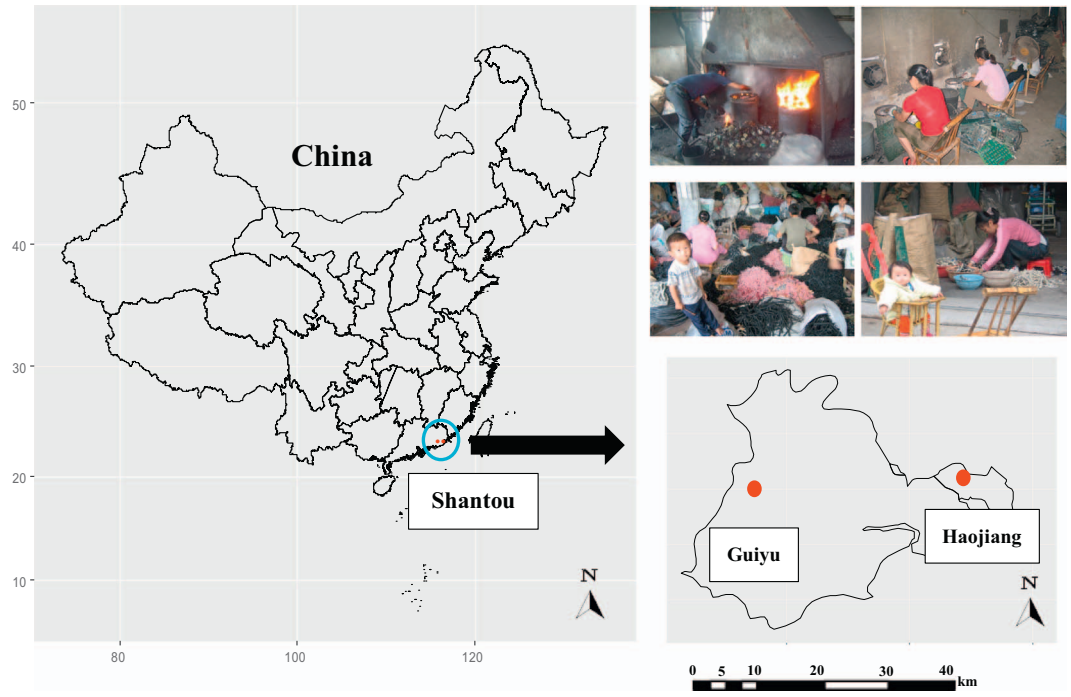

Fig. 1. Location of the study areas.

family history of disease, dietary habits, occupational history, smoking status, household income and education.

Taking into account that age and gender of the participants greatly impacts this research, we adopted a matching design according to age and gender, and then tested two biomarkers (plasma epinephrine and norepinephrine) of SAM activity in matching preschool children. Integrity of the questionnaire and physical examination data, blood sample volume, heart rate data, without disease and taking medicine were also important considerations for screening. Finally, the number of matching children from Guiyu and Haojiang was 107 children, respectively (3 years: n = 15; 4 years: n = 39; 5 years: n = 36; 6 years: n = 17). The detailed information is provided in Table 1.

2.2. Blood sample collection and analysis

A sample of venous blood was obtained from each child and collected in a Pb-free tube, containing EDTA as an anticoagulant, by well-trained nurses at the kindergartens. Blood samples were placed on ice and transported to the laboratory. One EDTA tube of blood was spun at 3000*g* for 15 min at 4 °C, then 300 μL of the plasma was stored at −70 °C until assay for norepinephrine and epinephrine.

Plasma norepinephrine and epinephrine were subsequently determined using an ELISA kit (DEE6500 2-CAT, Demeditec Diagnostics GmbH, Kiel, Germany) according to the manufacturer's instructions, as described by prior investigators (Bada et al., 2012). Threshold sensitivities for plasma norepinephrine and epinephrine were 36 pg/mL and 10 pg/mL, respectively. Measuring ranges for plasma norepinephrine and epinephrine were 93–33,333 pg/mL and 18–6667 pg/mL, respectively.

2.3. Heart rate measurements

Each participant was escorted to a quiet room by two assistants. Then, heart rate was measured by stethoscope (1 min) after a 15-minute rest in a chair. Measurements of heart rate were performed by one researcher — a medical doctor trained according to the study protocol. Two measurements were performed separated by a five-minute interval. If the difference between measurements exceeded 5 bpm/min, a third measurement was performed. Children were not allowed to run and talk during the session.

2.4. Air pollutants and meteorological parameters

An increasing number of studies show that the pollution data, based on air monitoring stations, have the potential to fill the air pollution exposure gaps in the field of environmental health research and could be assessed or calculated for the daily exposure of each participant (e.g. ≤15-km radius) (Delfino et al., 2002; Wiwatanadate, 2014; Darrow et al., 2011; Iskandar et al., 2012). In our study, daily data for air pollution (the Chaonan air quality monitoring station and the Haojiang air quality monitoring station) and meteorological parameters came from the Ministry of National Environmental Protection (http://106.37.208.233:20035) and the National Meteorological Information Center (http://data.cma.cn) and were collected from July to December 2016. Data included $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, O_3, temperature and humidity. All participants in Guiyu lived within an 8-km radius of the Chaonan air quality monitoring station, and all participants in Haojiang lived within an 8-km radius of the Haojiang air quality monitoring station, which was estimated by the study participants individual home and school address and geographic coordinates of the air quality monitoring station, consistent with other studies (Delfino et al., 2002; Wiwatanadate, 2014). Our prior study found that among the people living in Guiyu, nearly 60–80% of families engaged in e-waste recycling operations conducted in small-scale family-run workshops in the front and backyards of homes (Huo et al., 2007; Zheng et al., 2016). The kindergartens were built in the living area in both Guiyu and Haojiang.

2.5. Statistical methods

Statistical analyses were performed with SPSS19.0, Graph Pad Prism 6.0, and Genstat 18.0 software. Descriptive statistics were presented as mean values ± standard deviation (SD) for numeric variables, or as percent (relative numbers) for categorical variables. Differences between groups were analyzed by an independent-sample *t*-test when the two sets of data were distributed normally. The Mann-Whitney *U* test was used for two-group comparisons of non-normally

Table 1
Demographic characteristics of the Guiyu and Haojiang study populations.

Characteristics	Exposed group	Reference group	Statistics	p
Age (years)				
Total (n = 423) (mean ± SD)	4.61 ± 0.91	4.44 ± 1.03	$t = -1.77$	0.077
Match (n = 214) (mean ± SD)	4.51 ± 0.93	4.51 ± 0.93	$t = 1.000$	1.000
3 years (male/female)	7/8	7/8	$\chi^2 = 0.000$	1.000
4 years (male/female)	23/16	23/16	$\chi^2 = 0.000$	1.000
5 years (male/female)	18/18	18/18	$\chi^2 = 0.000$	1.000
6 years (male/female)	11/6	11/6	$\chi^2 = 0.000$	1.000
Gender				
Total (male/female)	119/109	115/80	$\chi^2 = 1.956$	0.162
Match (male/female)	59/48	59/48	$\chi^2 = 0.000$	1.000
Family history of hypertension [n (%)]	71(31.7)	55(28.2)	$\chi^2 = 0.450$	0.503
Family history of diabetes [n (%)]	18(9.2)	38(17.0)	$\chi^2 = 4.737$	0.030
Eating fruits or vegetables				
Every day	97 (43.0)	158 (81.0)	$\chi^2 = 64.392$	< 0.001
1–3 times a week	115 (50.9)	35 (18.0)		
1–3 times a month	9 (4.0)	1 (0.5)		
< 1 times a month	5 (2.2)	1 (0.5)		
Family member daily smoking [n (%)]				
Non-smoking	56 (25.6)	99 (51.0)	$\chi^2 = 38.754$	< 0.001
~2 cigarettes	30 (13.4)	24 (12.4)		
~10 cigarettes	70 (32.0)	27 (14.0)		
~20 cigarettes	44 (20.1)	39 (20.1)		
> 20 cigarettes	19 (8.7)	5 (2.6)		
Paternal work associated with e-waste dismantling (yes/no)	49/170	2/192	$\chi^2 = 43.296$	< 0.001
Ventilation of house (yes/no)	188/32	191/4	$\chi^2 = 20.369$	< 0.001
E-waste contamination within 50 m away from residence (yes/no)	62/150	2/185	$\chi^2 = 58.570$	< 0.001
Distance of residence from road (m) [n (%)]			$\chi^2 = 91.061$	< 0.001
< 10	84 (38.9)	10 (5.2)		
~50	53 (24.5)	37 (19.2)		
~100	50 (23.1)	57 (29.5)		
> 100	29 (13.4)	89 (46.1)		
Monthly household income (yuan) [n (%)]				
< 1500	9 (4.6)	2 (1.1)	$\chi^2 = 29.164$	< 0.001
1500–3000	31 (15.9)	19 (10.0)		
3000–4500	59 (30.3)	31 (16.3)		
4500–6000	41 (21.0)	38 (20)		
> 6000	55 (28.2)	100 (52.6)		
Maternal education levels [n (%)]				
Primary school	28 (12.6)	6 (3.1)	$\chi^2 = 100.221$	< 0.001
Middle school	118 (53.2)	30 (15.5)		
Vocational school	31 (14.0)	41 (21.1)		
High school	15 (6.8)	26 (13.4)		
College/university	30 (13.5)	91 (46.9)		

distributed data; a chi-square test was used to compare categorical variables between different groups. The outliers and extreme values during analyses were deleted to ensure the match and comparability between two groups. The relationship between two sets of data with normal distribution was analyzed by Pearson correlation coefficients. Otherwise, the Spearman's correlation test was used. Confounding factors were adjusted, the generalized linear mixed model was used to estimate plasma epinephrine, plasma norepinephrine, heart rate and the relationship with air pollutant concentrations in the 24-hour period of the day of health examination (lag 0), in the 3 previous 24-hour periods before the health examination (lag 1–3), and in the 24-hour period after the health examination (lag 4), as well as the 30-day and the 4-month average of pollution before the health examination visit (lag 5–6). A probability level of < 0.05 was accepted as significant. All statistical tests requiring an assumption of normality were conducted on natural logarithmic-transformed concentrations.

3. Results

3.1. Demographic characteristics of the study population

The demographic characteristics of the 423 participants are summarized in Table 1. The average age of the children was 4.61 years (SD ± 0.91) in the e-waste recycling area and 4.44 years (SD ± 1.03) in the non-e-waste recycling area ($p > 0.05$). The gender distribution of children did not show significant differences between the e-waste recycling area and the non-e-waste recycling area ($p > 0.05$). A family history of hypertension was similar in both areas ($p > 0.05$). Significant differences between the two areas were found for family history of diabetes, fruit and vegetable consumption, smoking by a family member, paternal work associated with e-waste dismantling, distance of residence from road, housing ventilation, e-waste contamination within 50 m from the residence, monthly household income, and maternal education levels ($p < 0.05$).

3.2. Air pollutant concentrations and related factors

An independent sample t-test was performed to assess differences in air pollutants between the e-waste recycling area and the non-e-waste recycling area (Fig. 2). Concentrations of $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO of the e-waste recycling area were significantly higher (all $p < 0.001$), whereas O_3 was significantly lower compared to the non-e-waste recycling area atmosphere ($p < 0.05$).

Throughout the study period, several pairs of pollutants were moderate to highly correlated ($r > 0.5$) ($PM_{2.5}$ and PM_{10}; SO_2 and PM_{10}; NO_2 and $PM_{2.5}$, PM_{10}, SO_2, respectively; CO and $PM_{2.5}$, PM_{10}, SO_2, NO_2, respectively). O_3 was negatively correlated with NO_2 ($r_s = -0.232$, $p < 0.01$) and CO ($r_s = -0.143$, $p < 0.01$), but was

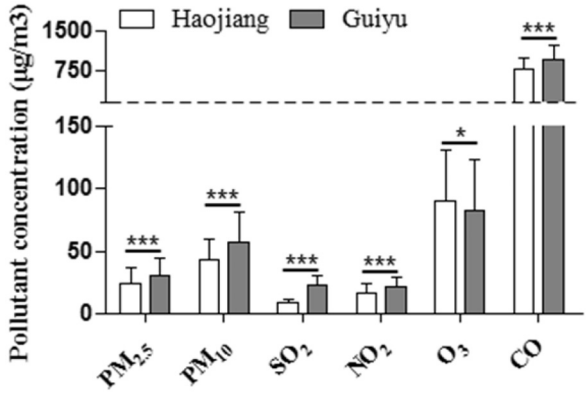

Fig. 2. Distributions of 24-hour mean concentrations of air pollutants. Data analysis by the independent sample *t*-test. ***Significant at $p < 0.001$.**Significant at $p < 0.01$. *Significant at $p < 0.05$.

weakly correlated with SO_2. In addition, correlations among air pollutants and temperature and relative humidity were found (Table 2).

3.3. Distributions in heart rate, plasma norepinephrine and epinephrine

Heart rate and plasma norepinephrine and epinephrine were analyzed, including children of different ages living in the e-waste recycling area, and native and non-native children living in the non-e-waste recycling area (in the e-waste recycling area, native and non-native children were not disassembled for further analysis, as only 9 children are non-native children) (Fig.3).

3.3.1. Heart rate

The highest median level of heart rate was obtained in the e-waste recycling area (median: 106 bpm/min), followed by (in decreasing order) native children living in the non-e-waste recycling area (median: 102 bpm/min) and non-native children living in the non-e-waste recycling area (median: 100 bpm/min) (Fig. 3a). No significant difference was found in heart rate between native children and non-native children living in the non-e-waste recycling area ($p > 0.05$) (Fig. 3a). However, the heart rate in children from the e-waste recycling area was significantly higher compared to either all children in the non-e-waste recycling area (total) ($p < 0.01$), native children living in the non-e-waste recycling area ($p < 0.05$), or non-native children living in the non-e-waste recycling area ($p < 0.001$) (Fig. 3a). Both 3-year-old and 4-year-old children living in the e-waste recycling area had significantly higher heart rate than those living in the non-e-waste recycling area (all $p < 0.01$) (Fig.3a).

3.3.2. Plasma norepinephrine and epinephrine

Children living in the e-waste recycling area had significantly higher plasma norepinephrine concentrations than those from the non-e-waste recycling area ($p < 0.01$) (Fig. 3c). Furthermore, plasma norepinephrine concentrations in children from an e-waste recycling area were significantly higher than in native children living in the non-e-waste recycling area ($p < 0.01$) or non-native children living in the non-e-waste recycling area ($p < 0.05$) (Fig. 3c). The concentrations of plasma norepinephrine were in the following order: children living in an e-waste recycling area (median: 4.425 nmol/L) > non-native children living in the non-e-waste recycling area (median: 3.885 nmol/L) > native children living in the non-e-waste recycling area (median: 3.444 nmol/L) (Fig. 3c). No significant difference was found in plasma norepinephrine between native children and non-native children living in the non-e-waste recycling area ($p > 0.05$) (Fig. 3b). We also stratified by age and analyzed the differences of plasma norepinephrine between the e-waste recycling area and the non-e-waste recycling area. Concentrations of plasma norepinephrine were found to be higher in children from the e-waste recycling area than from the non-e-waste recycling area in 4-year-old and 6-year-old children (all $p < 0.05$) (Fig. 3c). However, concentrations of plasma epinephrine of children living in an e-waste recycling area exhibited no significant changes, compared with children living in the non-e-waste recycling area, when either total or stratified data were examined (all $p > 0.05$) (Fig. 3b).

3.4. Heart rate, norepinephrine, epinephrine and the relationships to air pollutants

A generalized linear mixed model was used to estimate the relationships between heart rate, plasma norepinephrine, epinephrine and outdoor air pollutant concentration on the 24-h of the day of the health examination (lag 0), in the 3 previous 24 h before the health examination (lag 1–3), in the 24 h after the health examination (lag 4) and the 30-day and 4-month average of pollution before the health examination visit (lag 5–6) in the entire group of children (Table 3). $PM_{2.5}$, PM_{10}, SO_2 and NO_2 concentrations in the 30 days and in the 4 months before the health examination showed a positive association with plasma norepinephrine level. CO concentrations in the 4 months before the health examination showed a positive association with plasma norepinephrine level. $PM_{2.5}$, PM_{10}, SO_2, NO_2 and CO concentrations on the day of health examination visit (lag 0), in the 3 previous 24-hour periods before the health examination and the 24-hour period after the health examination were related to disadvantageous changes in heart rate. In addition, there were negative associations between plasma norepinephrine and CO concentrations in the three 24-hour periods before the health examination (lag 1–3). However, no significant relationships were observed between the level of $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3 and plasma epinephrine.

Table 2
Spearman correlation coefficients for air pollutants, ambient temperature, and relative humidity, measured on a 24-hour average basis.

	$PM_{2.5}$	PM_{10}	SO_2	NO_2	CO	O_3	Temperature	Humidity
No. of 24-h periods	368	368	368	368	368	368	368	368
$PM_{2.5}$	1							
PM_{10}	**0.950****	1						
SO_2	**0.481****	**0.554****	1					
NO_2	**0.577****	**0.594****	**0.524****	1				
CO	**0.549****	**0.579****	**0.550****	**0.661****	1			
O_3	**0.263****	**0.215****	−0.016	**−0.232****	**−0.143****	1		
Temperature	**−0.175****	**−0.173****	0.065	**−0.475****	**−0.393***	**0.437****	1	
Humidity	**−0.342***	**−0.344***	−0.101	**−0.212****	−0.073	**−0.295****	0.099	1

Significant p-values ($p < 0.05$.) are marked in bold.
** Significant at $p < 0.01$.
* Significant at $p < 0.05$.

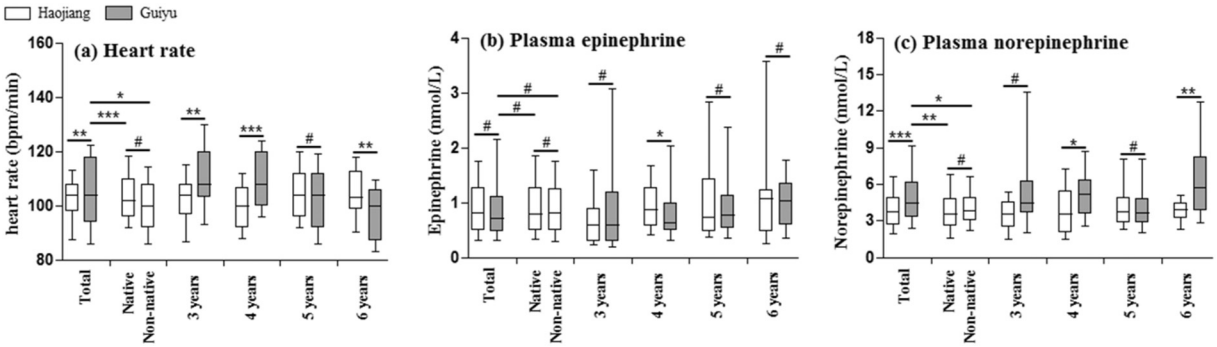

Fig. 3. Levels of heart rate, plasma epinephrine and plasma norepinephrine from the e-waste recycling area (Guiyu) and the non-e-waste recycling area (Haojiang). Data analysis by the Mann-Whitney *U* test. ***Significant at $p < 0.001$.**Significant at $p < 0.01$. *Significant at $p < 0.05$. #Significant at $p > 0.05$.

3.5. Effect of e-waste air pollutants exposure on norepinephrine, epinephrine and heart rate

To further investigate the effect of air pollutant exposure on the SAM system, based on e-waste recycling and dismantling activities, we defined participants living within a 50-m radius of family-run workshops or frequent contact with e-waste dismantling activities as the high air pollution group, and participants living further than a 50-m radius of family-run workshops and were not in contact with e-waste dismantling activities were defined as the low air pollution group, and then regrouped the children from both regions (the e-waste recycling area and the non-e-waste recycling area) for comparing plasma norepinephrine and epinephrine levels and heart rate.

3.5.1. Effect of e-waste air pollution exposure on plasma norepinephrine and epinephrine levels

The concentration of plasma norepinephrine in children from the high air pollution group (median: 4.45 nmol/L; range: 0.76 to 17.78) was higher than children from the low air pollution group (median: 3.86 nmol/L; range: 0.51 to 16.86) ($p < 0.05$) (Fig. 4). In addition, there was no significant difference in plasma epinephrine concentrations between children exposed to high air pollution (median: 0.77 nmol/L; range: 0.10 to 2.93) vs. low air pollution (median: 0.75 nmol/L; range: 0.15 to 4.93) ($p > 0.05$).

3.5.2. Comparison of child heart rate between two groups

An independent sample *t*-test showed that heart rate in children from the high air pollution group (104.99 ± 13.65 bpm/min) was higher than children from the low air pollution group (102.42 ± 10.90 bpm/min) ($t = -0.245$, $p < 0.05$) (Fig. 5).

4. Discussion

The main aim of this study was to investigate the correlation between air pollutant exposure and the SAM system of preschool children living in an e-waste recycling area. We characterized the changes of two plasma biomarkers of the SAM system, and heart rate, and explored the association of changes in the SAM system with air pollutant exposure in preschool children from Guiyu, a typical e-waste recycling area. Results show moderate to large increases in all air pollutants, except for ozone, and that temperature and humidity are negatively related to air pollutant levels. Similar findings on these pollution changes and their relationships with meteorological parameters have been previously reported in other air-polluted areas of China (Rich et al., 2012). Previous studies have also shown that in China, most e-waste recycling operations are primitive and informal, e.g. open-air burning, melting over coal grills, free acid washing, and dumping remnant residue and ash, resulting in several toxicants being associated with solid particles, liquid droplets, or gasses released into ambient atmosphere (Xu, X. et al., 2015a; Zhang et al., 2016).

Concomitantly, levels of plasma norepinephrine, a biomarker of SAM activity, and heart rate are increased in children living in an e-waste recycling area. There is no difference in plasma norepinephrine and heart rate between native and non-native children living in the non-e-waste recycling area, suggesting the importance of e-waste in influencing plasma norepinephrine and heart rate changes in children. In addition, analysis of related factors shows that plasma norepinephrine and heart rate positively correlate with air pollution ($PM_{2.5}$, PM_{10}, SO_2, NO_2), indicating that air pollution exposure is a risk factor that could interfere with the SAM system in children. However, there are numerous toxic pollutants in e-waste recycling areas, in addition to air pollutants, that might affect child heart rate and plasma norepinephrine. Furthermore, a prior study showed that for risk, the comparisons and analysis based on cutoff value (in strata or tiers) could be better than the statistical analysis based on mean comparisons and percentage increases (Rich et al., 2012). An increasing number of studies show that the distance between the participants' homes and outdoor air pollution sources (e.g. road traffic and mines) could be used to calculate and evaluate the level of air pollution exposure (Blount et al., 2017; Clark et al., 2017; Dell et al., 2014). To further determine the effect of air pollution exposure based on e-waste recycling and dismantling activities on the SAM system in children, we categorized participants living within a 50-m radius of family-run workshops or having frequent contact with e-waste dismantling activities as the high air pollution group. The results, after regrouping children into high and low categories, show that plasma norepinephrine and heart rate in children exposed to high air pollution levels are both significantly higher than in children exposed to low air pollution levels, further suggesting the adverse effect of air pollutant exposure based on e-waste recycling and dismantling activities on the SAM system. Together, the above findings suggest that air pollution exposure in e-waste recycling and dismantling areas results in SAM dysfunction in preschool children. It is well known that in the central nervous system (CNS), SAM activation is accomplished by alteration of presynaptic alpha 2-adrenergic receptors, which are vital in determining central catecholamine (including norepinephrine and epinephrine) levels and activation, and adrenergic alpha 2-adrenergic receptors are almost completely expressed in the CNS (MacMillan et al., 1996; Makaritsis et al., 1999; Makaritsis et al., 2000; Ying et al., 2014). It has been shown that the development of the nervous system and expression of presynaptic receptors of children is less mature, and air pollutants and other pollution exposure have adverse effects on nervous system development in children, and environmental toxins have been shown to affect presynaptic neurochemical changes (Liu and Pope, 1998; Saenen et al., 2015; Schelb et al., 2001; Zhang et al., 2017), as well as lead to impairment of cholinergic and dopaminergic transmission and environmental toxin-induced oxidative stress, and contribute to increases in sympathetic activity via other central mechanisms (Bielarczyk et al., 1996; Bourjeily and Suszkiw, 1997; Brockel and Cory-Slechta, 1999).

To investigate the effect of exposure to air pollution during different

Table 3
Relationships of plasma epinephrine, plasma norepinephrine and heart rate with air pollutant concentrations.

	Epinephrine			Norepinephrine			Heart rate		
	β-Value	SE	p-Value	β-Value	SE	p-Value	β-Value	SE	p-Value
$PM_{2.5}$									
Lag 0	0.0056	0.0053	0.325	−0.0051	0.0047	0.282	0.0026	0.0021	0.151
Lag 1	−0.0111	0.0063	0.050	−0.0065	0.0056	0.257	0.0000	0.0025	0.909
Lag 2	0.0031	0.0040	0.730	−0.0025	0.0035	0.606	**0.0071**	**0.0018**	**< 0.001**
Lag 3	−0.0014	0.0046	0.484	−0.0001	0.0039	0.944	**0.0053**	**0.0018**	**0.012**
Lag 4	0.0071	0.0042	0.130	−0.0046	0.0042	0.260	**−0.0019**	**0.0016**	**0.044**
Lag 5	−0.0143	0.0130	0.325	**0.0355**	**0.0104**	**0.001**	−0.0025	0.0023	0.471
Lag 6	−0.0318	0.0206	0.124	**0.0591**	**0.0169**	**< 0.001**	0.0031	0.0024	0.196
PM_{10}									
Lag 0	0.0000	0.0027	0.833	−0.0023	0.0024	0.287	−0.0000	0.0010	0.452
Lag 1	−0.0079	0.0053	0.118	−0.0043	0.0044	0.348	**0.0031**	**0.0021**	**0.023**
Lag 2	−0.0004	0.0024	0.610	−0.0021	0.0020	0.342	**0.0027**	**0.0010**	**0.009**
Lag 3	−0.0031	0.0027	0.182	−0.0001	0.0024	0.945	**0.0024**	**0.0010**	**0.014**
Lag 4	0.0029	0.0031	0.351	−0.0015	0.0028	0.510	−0.0015	0.0011	0.219
Lag 5	−0.0072	0.0058	0.258	**0.0160**	**0.0046**	**0.001**	−0.0006	0.0010	0.913
Lag 6	−0.0147	0.0091	0.108	**0.0264**	**0.0075**	**< 0.001**	0.0015	0.0011	0.150
SO_2									
Lag 0	−0.0140	0.0017	0.659	0.0065	0.0118	0.772	**0.0037**	**0.0038**	**0.004**
Lag 1	−0.0322	0.0109	0.054	0.0044	0.0124	0.964	−0.0099	0.0053	0.382
Lag 2	0.0013	0.0135	0.935	−0.0035	0.0114	0.799	**0.0228**	**0.0055**	**< 0.001**
Lag 3	−0.0077	0.0147	0.725	0.0176	0.0124	0.171	**0.0298**	**0.0065**	**< 0.001**
Lag 4	−0.0353	0.0139	0.095	−0.0020	0.0142	0.692	−0.0067	0.0057	0.927
Lag 5	−0.0139	0.0118	0.248	**0.0337**	**0.0096**	**0.001**	0.0054	0.0023	0.095
Lag 6	−0.0134	0.0087	0.128	**0.0255**	**0.0072**	**< 0.001**	**0.0050**	**0.0020**	**0.027**
NO_2									
Lag 0	0.0021	0.0090	0.405	0.0094	0.0082	0.376	−0.0008	0.0032	0.430
Lag 1	−0.0312	0.0134	0.144	0.0098	0.0139	0.708	−0.0174	0.0061	0.053
Lag 2	0.0383	0.0253	0.165	−0.0190	0.0230	0.440	**0.0233**	**0.0102**	**0.017**
Lag 3	−0.0312	0.0129	0.108	**0.0384**	**0.0112**	**< 0.001**	**0.0080**	**0.0050**	**< 0.001**
Lag 4	−0.0241	0.0105	0.155	0.0073	0.0122	0.760	**0.0020**	**0.0038**	**0.019**
Lag 5	−0.0280	0.0212	0.240	**0.0518**	**0.01845**	**0.011**	0.0036	0.0037	0.678
Lag 6	−0.0420	0.0242	0.084	**0.0676**	**0.0199**	**< 0.001**	0.0030	0.0028	0.294
CO									
Lag 0	−0.4575	0.4871	0.761	0.0200	0.4490	0.857	0.0487	0.1630	0.104
Lag 1	**−1.5670**	**0.4483**	**0.007**	−0.0018	0.4857	0.802	**−0.6902**	**0.2060**	**0.007**
Lag 2	**−1.2350**	**0.4972**	**0.022**	−0.5581	0.4389	0.155	**−0.4972**	**0.1853**	**0.047**
Lag 3	**−1.6940**	**0.5009**	**0.012**	0.2672	0.6356	0.830	−0.2871	0.26704	0.780
Lag 4	−0.4194	0.3289	0.573	0.0527	0.3195	0.945	**0.0724**	**0.1062**	**0.009**
Lag 5	−0.9172	0.7369	0.281	1.1450	0.7548	0.257	−0.7854	0.3861	0.127
Lag 6	−1.8350	1.0018	0.073	**2.7560**	**0.8394**	**0.001**	0.0971	0.1179	0.411
O_3									
Lag 0	−0.0052	0.0042	0.141	−0.0091	0.0003	0.018	**−0.0036**	**0.0014**	**< 0.001**
Lag 1	0.0007	0.0028	0.941	−0.0044	0.0023	0.073	0.0010	0.0011	0.467
Lag 2	0.0085	0.0033	0.053	−0.0009	0.0032	0.996	**0.0061**	**0.0014**	**< 0.001**
Lag 3	0.0041	0.0022	0.294	−0.0027	0.0022	0.380	**0.0032**	**0.0011**	**0.021**
Lag 4	−0.0028	0.0035	0.220	**−0.0081**	**0.0022**	**< 0.001**	**−0.0021**	**0.0010**	**< 0.001**
Lag 5	−0.0035	0.0034	0.258	−0.0197	0.0175	0.419	**−0.0159**	**0.0054**	**< 0.001**
Lag 6	0.0345	0.0197	0.082	−0.0227	0.0222	0.317	0.0047	0.0032	0.147

Lag 0: the day of health examination; Lag 1: previous day; Lag 2: two days prior; Lag 3: three days prior; Lag 4: the day after; Lag 5: previous 30-day period; Lag 6: previous 4-month period.
Data analysis based on a generalized linear mixed model in the entire group of children.
One random effect per subject and area.
Adjustments: data adjusted by gender, age and family history (hypertension and diabetes), education, income, smoking history, vegetable and fruit consumption.
Significant p-values ($p < 0.05$.) are marked in bold.

periods, we analyzed the air pollutant concentrations in the 24-hour period of the day of the health examination (lag 0), in the 3 previous 24 h before (lag 1–3), an in the 24-hour period after (lag 4) and in the 30-day and 4-month period before the examination (lag 5–6). Some of the lag patterns shown in Table 5 are intriguing. The changes in plasma norepinephrine associated with the previous 30-day and 4-month mean concentrations of air pollutants are consistent with findings showing impairment of autonomic regulation of cardiovascular homeostasis associated with repeated ambient $PM_{2.5}$ exposure in a rat model (Carll et al., 2017). Previous systematic reviews show that long-term exposure to air pollution and particulate matter contributes to the development and progression of cardiovascular events by affecting the autonomic nervous system (Fiordelisi et al., 2017). Prolonged passive smoking (lasting 3 weeks) can impair plasma catecholamine levels, such as by increasing plasma norepinephrine levels (Torok et al., 2000). For heart rate, we demonstrate a short-term response to air pollutants (shown in the 24-hour mean concentration from the 3 previous days to the day after). A cohort study estimates that a short-term exposure to $PM_{2.5}$ increases the risk of cardiovascular events from 0.4 to 1.0%, and it is known that the cardiovascular system is highly vulnerable to short-term exposure to $PM_{2.5}$ (CA 3rd Pope 3rd et al., 2006; Schlesinger, 1990). The mechanisms for short-term, acute exposure to particulate matter can be attributed to an enhanced tendency for thrombosis, changes of endothelial function, increased response of systemic inflammation and activity of the autonomic nervous system (Bartoli et al., 2009; Cozzi et al., 2006; Fiordelisi et al., 2017; Rich et al., 2012; Du et al., 2016). In

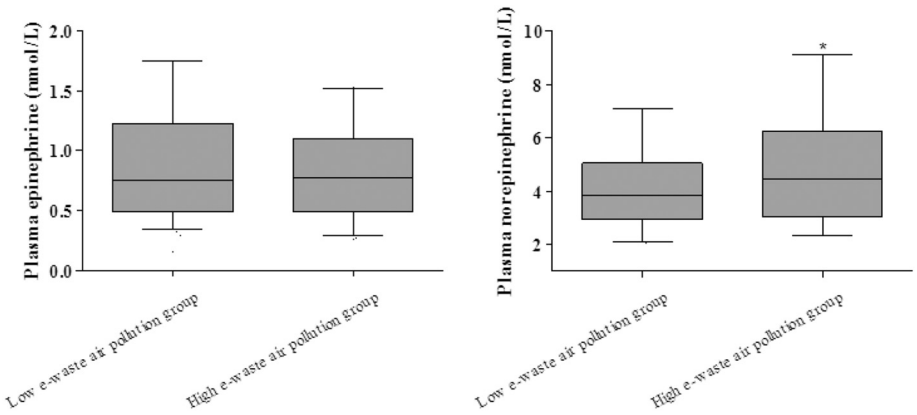

Fig. 4. Levels of plasma norepinephrine from the high e-waste air pollution level group were higher than from the low e-waste air pollution level group. Data analysis by the Mann-Whitney U test. *Significant at $p < 0.05$.
High e-waste air pollution group: participants living within a 50-m radius of family-run workshops or having frequent contact with e-waste dismantling activities; low e-waste air pollution group: participants living within further a 50-m radius of family-run workshops and not in contact with e-waste dismantling activities.

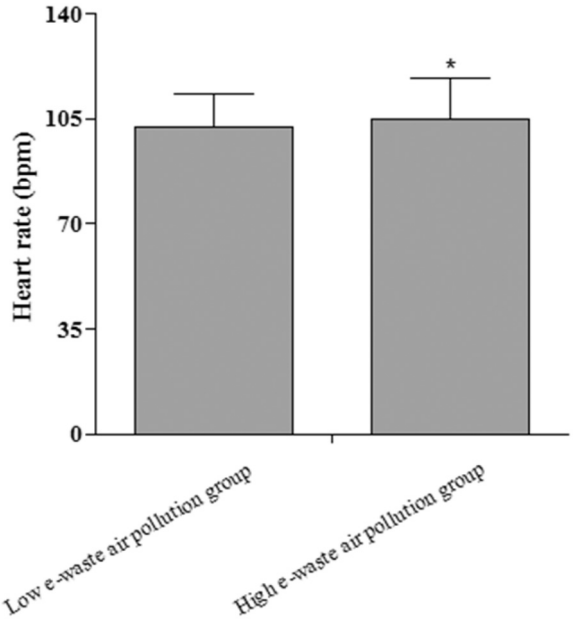

Fig. 5. Heart rate in the high e-waste air pollution group is higher than in the low e-waste air pollution group. Data analysis by the independent sample t-test. *Significant at $p < 0.05$.
High e-waste air pollution group: participants living within a 50-m radius of family-run workshops or having frequent contact with e-waste dismantling activities; low e-waste air pollution group: participants living further than a 50-m radius of family-run workshops and not in contact with e-waste dismantling activities.

addition, we show a gradual decrease in effect estimates of heart rate in the lag 2–4 periods ($PM_{2.5}$: lag 2–4; PM_{10}: lag 2–4; NO_2: lag 2–4 and O_3: lag 2–4). These effects could be ascribed to compensatory mechanisms responding to the changes in heart rate triggered by air pollution at early lags, or affected by repeat and long-term exposure to air pollution (Rich et al., 2012).

In addition, the findings from our reports also reflect the impacts of air pollution as a whole mixture, rather than as the impact based on one or more specific air pollutants, consistent with previous findings (Rich et al., 2012). A prior study identified the specific components of the air pollution mixture (e.g. gaseous pollutants vs. particulate pollutants) and what specific toxic components of particulate matter are more toxic and harmful than others (Delfino et al., 2009). Furthermore, correlations among air pollutants due in part to the simultaneous release of multiple pollutants during dismantling of e-waste, make it difficult to differentiate effects of individual pollutants or pollutant sources. Our study shows that SO_2 and NO_2 and PM could result in an increase in heart rate and plasma norepinephrine. The seemingly beneficial effects of O_3 on plasma biomarkers of SAM activity and heart rate is likely due to its negative correlations with SO_2, NO_2 and other air pollutants (PM), as was similarly observed in previous studies (Anderson et al., 1998; Hajat et al., 1999; Rich et al., 2012). Previous studies suggest that short-term exposure to medium and high ambient concentrations of O_3 affect response of systemic inflammation and activity of the autonomic nervous system that may contribute to adverse cardiovascular events (Arjomandi et al., 2015). Long-term exposure to O_3 could affect activity of peripheral and central catecholamine and produce remarkable neural disturbances in rats (Cottet-Emard et al., 1997).

Clinical and epidemiological associations of ambient air pollution as an risk factor for numerous CVD events, including acute cardiovascular events (e.g. stroke, coronary events, myocardial infarction and cerebrovascular events) and chronic cardiovascular events (e.g., atherosclerosis and deep vein thrombosis), are largely driven by the adult and elderly and people with CVD, which has been preliminarily summarized in prior studies (Pope et al., 2015; Gerber et al., 2014; Rich et al., 2012; Mateen and Brook, 2011; Baccarelli et al., 2008; Miller et al., 2007). In our studies, we observed ambient air pollution exposure is associated with SAM biomarker changes of preschool children living in an e-waste recycling and dismantling area. This could be particularly important as the body development of children is less mature and vulnerable to environmental factors, and chronic effects of cardiovascular regulatory changes that begin at earlier ages, especially in childhood, convey CVD risk at older ages (Feinstein and Quivers, 1997; Cong et al., 2017).

Although this study has several strengths, including a large range of pollutant concentrations across the study period and a relatively large sample size, there are several limitations that should be noted when interpreting our results. First, we did not measure each participant's personal exposure to each air pollutant (including PM toxic components) and instead used air pollution data coming from the Ministry of National Environmental Protection, which might not adequately reflect individual exposures and result in underestimates of pollutant-mediated biomarker and cardiovascular physiology parameter changes. Furthermore, other cardiovascular physiology parameters and other potential biomarkers need to be explored in e-waste recycling areas, such as blood pressure of local children and biomarkers of inflammation and thrombosis, and whether such adverse effects found in our study remain associated.

5. Conclusion

Overall, the results of our present study show a clear adverse effect of air pollution on plasma norepinephrine and heart rate in preschool children from an e-waste recycling area, and suggest that air pollution in the e-waste recycling area results in SAM dysfunction of preschool children. The current study provides a scientific basis for further study concerning the effect of air pollutant exposure on development of the child cardiovascular system. In addition, environmental air pollution still threatens the health of children, despite recent reductions in the

pollution of e-waste-polluted areas. Stronger management measures of the related government sectors and preventive measures for people, especially children who are at a critical period of growth, are therefore essential in the e-waste recycling area.

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