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Four-year population exposure study: Implications for the effectiveness of e-waste control and biomarkers of e-waste pollution

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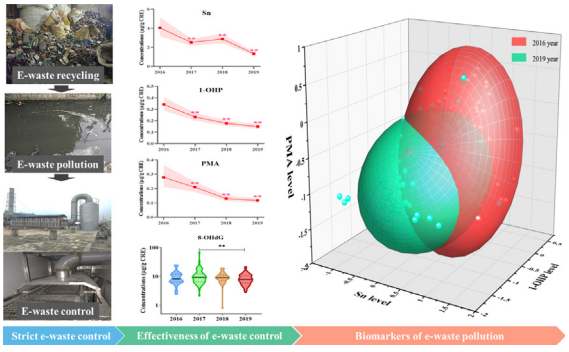
HIGHLIGHTS

- E-waste control can reduce human exposure to PAHs, VOCs and some heavy metals.
- E-waste control can significantly reduce oxidative DNA damage in the human body.
- Urinary Sn, PMA and 1-OHP are potential biomarkers of e-waste pollution or control.
- Children are more vulnerable to e-waste pollution than adults.

GRAPHICAL ABSTRACT



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ABSTRACT

E-waste pollution has emerged as a significant environmental concern. To assess the impact of e-waste control on human pollutant exposure risk and identify appropriate biomarkers to classify e-waste pollution levels, we performed longitudinal population exposure monitoring research in an e-waste recycling area in China after e-waste control. The urinary levels of oxidative stress markers and typical pollutants emitted during e-waste recycling, including heavy metals, polycyclic aromatic hydrocarbons (PAHs), and volatile organic compounds (VOCs), were continuously monitored in the surrounding population (including 275 children and 485 adults) from 2016 to 2019 using high-performance liquid chromatography-tandem mass spectrometry and inductively coupled plasma–mass spectrometry. The results showed that exposure to PAHs, VOCs and heavy metals was significantly associated with oxidative stress levels in urine. After e-waste control, the exposure levels of most PAHs and VOCs and a few heavy metals in the population significantly decreased. Interestingly, the level of 8-hydroxy-2′-deoxyguanosine (a biomarker of oxidative DNA damage) in children significantly decreased by 17.6 %, from 9.45 μg/g CRE in 2017 to 7.79 μg/g CRE in 2019 ($p < 0.01$). Thus, implementing e-waste control measures effectively reduced the human exposure risk to e-waste pollutants. Urinary tin (Sn), *s*-phenylmercapturic acid (PMA), 2-&3-hydroxyfluorene (2-&3-OHF), 3-hydroxyphenanthrene (3-OHPhe), and 1-hydroxypyrene (1-OHP) levels decreased significantly and monotonically over time ($p < 0.01$). The levels of urinary Sn and PMA in combination with 1-OHP, 2-&3-OHF, or 3-OHPhe as biomarkers demonstrated an excellent ability to classify e-waste pollution. These biomarkers will facilitate evaluations of the effectiveness of the governmental pollution regulations and policy measures. Additionally, children were

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generally exposed to higher levels of heavy metals and VOCs and suffered higher levels of oxidative stress damage than adults, suggesting that children are more vulnerable to e-waste pollution. This work will provide a reference for e-waste management and control.

1. Introduction

Electronic waste (e-waste) refers to waste electrical and electronic equipment, including computers, mobile phones, washing machines, air conditioners, and televisions, and it is composed of sophisticated blends of plastics, metals, and other materials (Xu et al., 2015). Global e-waste production increased from 41.8 million tons (Mt) in 2014 to 53.6 Mt in 2019, and it is expected to continue increasing to 74.7 Mt in 2030 at an annual growth rate of 2 Mt (Ahirwar and Tripathi, 2021). E-waste recycling represents a valuable tool for minimizing mountain-sized piles of e-waste and supplementing the shortage of certain primary resources. However, the current global trend of e-waste management has become unsustainable because <20 % of the worldwide e-waste produced in 2019 has reached formal waste management or recycling systems (Forti et al., 2020). The remainder was either disposed of in illegal landfills or informally recycled by workers; thus, e-waste pollution has emerged as a significant environmental concern. Currently, >1000 harmful substances have been identified as components of e-waste or byproducts generated in the e-waste dismantling process (WHO, 2021).

The sampling site of this study is a world-famous and typical e-waste dismantling site located in southern China, and it has an e-waste dismantling history that extends for >40 years. Informal processing of e-waste through open burning, heating, and acid leaching to extract precious metals has exposed the local population to a range of hazardous compounds, including heavy metals, such as lead (Pb) and cadmium (Cd), as well as toxic byproducts, such as polycyclic aromatic hydrocarbons (PAHs) and volatile organic compounds (VOCs) (MEE, 2019; WHO, 2021). The concentrations of some heavy metals and PAHs in soil or atmospheric particulate matter in the e-waste dismantling area are several times to tens of times higher than those in the reference area (Awasthi et al., 2018; Deng et al., 2006; Nie et al., 2015; Xiao et al., 2020; Yu et al., 2006). Several studies have indicated that urinary exposure levels of pollutants, including hydroxylated PAHs (OH-PAHs), heavy metals, and bisphenol, are positively associated with the levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG, a biomarker of oxidative DNA damage) and malonaldehyde (MDA, a biomarker of lipid damage) in e-waste-exposed populations (Lu et al., 2016; Parvez et al., 2021; Zhang et al., 2019), suggesting that 8-OHdG and MDA may represent comprehensive indicators of the health risks of e-waste dismantling activities to local populations. Epidemiological studies have shown that exposure to PAHs, Cd, and Pb in e-waste recycling areas is associated with changes in thyroid function, altered cellular expression and function, adverse neonatal effects, cognitive and behavioral changes and decreased lung function (Huo et al., 2019; Parvez et al., 2021). In addition, large quantities of VOCs with a low dielectric constant (e.g., benzene and toluene) generated during e-waste incineration are difficult to degrade, even with the use of advanced photocatalytic techniques, and they pose both cancer and noncancer risks to e-waste recycling workers (An et al., 2014; Liu et al., 2017).

The adverse health outcomes of e-waste recycling have been subjects of significant concern by local governments for decades (Deng et al., 2006). Strict e-waste management measures were implemented in an e-waste recycling area located in southern China in 2015. The government abolished illegal picking, incineration, and other informal dismantling activities and constructed industrial parks for the centralized treatment of scattered pollution (MEE, 2019); thus, this case provides a unique experimental scenario to explore the impacts of e-waste control on human pollutant exposure and health risks. We hypothesized that pollutants that declined monotonically after e-waste control could be regarded as specific indicators of e-waste pollution. As PAHs, VOCs, and heavy metals are typical pollutants in e-waste dismantling sites, we simultaneously biomonitored the urinary levels of fourteen hydroxy metabolites of PAH and VOC, ten heavy metals, 8-OHdG and MDA from 2016 to 2019 in populations surrounding in this e-waste recycling area after e-waste control. Through continuous monitoring of pollutant exposure and oxidative damage, we aimed to (1) reveal the time trends of exposure and effect biomarkers after e-waste control and assess the effectiveness of e-waste control measures and (2) identify appropriate biomarkers to reflect the impact of e-waste dismantling activities on local environmental pollution and human exposure risk.

2. Materials and methods

2.1. Chemicals and reagents

All chemicals and reagents used in this study are provided in Text S1.

2.2. Subject recruitment and sample collection

This longitudinal population exposure study was approved by the Research Ethics Committee of South China Normal University (Approval No. SCNU-SLS-2016-001). Four consecutive years of sampling were performed in an e-waste recycling area in southern China. Text S2 shows detailed information on the e-waste recycling sites. A total of 760 volunteers were recruited. From 2016 to 2019, the sample sizes were 67, 107, 135, and 176 for adults and 25, 61, 65, and 124 for children. The detailed population recruitment procedures are as follows: population sampling was conducted in November of each year; children and adult residents who had been settled in this area for at least two years were randomly recruited annually; and the “family mode” integrated with the local social environment characteristics was implemented to recruit volunteers. The first step was to establish regular family sampling points scattered in the residential areas. These designated families were willing to participate in our research and helped recruit their relatives or friends living locally. Priority was given to the recruitment of healthy children aged 6–12 and adults in their families. This “family mode” pattern ensured the representativeness of sampling and facilitated the recruitment of a relatively stable population, especially children. As the trust and support of residents increased, the sample size increased from 92 in 2016 to 300 in 2019. Each volunteer provided signed informed consent and completed a questionnaire, which included items on gender, age, weight, height, years of residency, occupation, fried or barbecued food consumption, and smoking or passive smoking. The children's questionnaire also included maternal education level and maternal occupation. A spot urine sample was collected for each volunteer after breakfast at 10–12 a.m. The creatinine (CRE) level in fresh urine was determined by the Jaffe reaction method within 2 h after urine sample collection (Taussky and Kurzmann, 1954). Then, the samples were stored at −20 °C until sample pretreatment and chemical analysis.

2.3. Sample pretreatment and instrument analysis

Parent PAHs and VOCs and their corresponding urinary metabolites are shown in Table S1. The levels of urinary 8-OHdG and 10 PAH metabolites, including 1-hydroxynaphthalene (1-OHN), 2-OHN, 2-hydroxyfluorene (2-OHF), 3-OHF, 1-hydroxyphenanthrene (1-OHPhe), 2-OHPhe, 3-OHPhe, 4-OHPhe, 9-OHPhe and 1-hydroxypyrene (1-OHP), were simultaneously determined using high-performance liquid chromatography-tandem mass spectrometry (HPLC–MS/MS) according to our previously described method with minor modifications (Fan et al., 2012). The specific sample pretreatment procedures are shown in Text S3. The levels of 4 urinary VOC metabolites, including *trans*,*trans*-muconic acid (MU), 1,2-dihydroxybenzene (1,2-DB),

s-phenylmercapturic acid (PMA), and *s*-benzylmercapturic acid (BMA), were simultaneously determined using HPLC–MS/MS according to our previous method after replacing the C18 cartridge with a polar-enhanced polymer cartridge (Fan et al., 2015). Ten urinary heavy metals, including chromium (Cr), manganese (Mn), cobalt (Co), nickel (Ni), copper (Cu), molybdenum (Mo), Cd, tin (Sn), barium (Ba), and Pb, were simultaneously determined using an inductively coupled plasma-mass spectrometer (ICP–MS) (Agilent 7800, USA). The direct dilution method was used for urine sample pretreatment, and the specific instrumental parameters have been described previously (Li et al., 2020). Briefly, urine samples were centrifuged at 13,000 rpm for 5 min. After filtering the urine supernatant using a 0.45 μm Millipore filter, 1.0 mL of urine was accurately transferred into a 10 mL polypropylene tube. Subsequently, 1.0 mL of internal standards and 8 mL of 2 % dilute nitric acid (v:v) were added. The mixed solution was used directly for instrumental analysis. The MDA concentration in urine was measured according to the protocol of a commercially available kit based on thiobarbituric acid reactivity. Briefly, 200 μL of urine was mixed with biochemical reagents and reacted at 95 °C for 40 min. Then, the red absorbance was measured at 532 nm with a microplate reader. All sample pretreatments and chemical measurements were conducted from 2019 to 2020.

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

Each batch consisted of two blank samples, six calibration curve samples, three QC samples (i.e., low, medium, and high concentrations of QC samples), and approximately 70 urine samples. A water blank and a procedure blank were prepared to examine the probable background contamination from reagents and sample pretreatments. To investigate the recovery and precision of the methods, three levels of QC samples were prepared by spiking native standards and isotope-internal standards into diluted pooled urine. Ten percent of randomly selected urine samples were analyzed in duplicate to evaluate the repeatability of the methods. The average linearity (R^2) of the calibration curves for all analytes was higher than 0.990 (Table S2). The average relative recoveries ranged from 84.3 % to 128 %, with relative standard deviations <15.0 % for all analytes (Table S2). Three QC samples were run before and after the analysis of urine samples. After analyzing every ten urine samples, the low QC sample was reanalyzed to verify the sensitivity of the instrument. The method detection limits (MDLs) were 0.10 μg/L for 8-OHdG and 7 μg/L for MDA. The MDLs ranged from 0.010 to 0.10 μg/L for PAH metabolites, 0.050 to 4.0 μg/L for VOC metabolites, and 0.10 to 3.0 μg/L for heavy metals (Text S4).

2.5. Statistical analysis

Statistical analyses were performed using SPSS (version 22.0, Chicago, IL, USA) and SAS (version 9.4, Cary, NC). Two-tailed *p* values ($p < 0.05$) were considered statistically significant. CRE was used to adjust the concentrations of urinary analytes before the statistical analysis. Rather than zero, MDL/√2 was used to replace those values below MDL. The Mann–Whitney *U* test was used to examine differences between two sets of continuous variables with abnormal distributions. The chi-squared test was used to examine differences between two or more groups of categorical variables. One-way analysis of variance was used to examine differences between multiple sets of continuous variables. Spearman's correlation analysis was used to evaluate the association of age with levels of pollutant exposure and oxidative stress. A multiple linear regression model was employed to assess the dose–response relationship between urinary pollutant exposure and oxidative stress levels. The regression model included age, sex, body mass index (BMI), sampling year, and population type (i.e., children and adults) as covariates due to their associations with pollutant exposure and oxidative stress levels. The results are presented as the regression coefficient (β) and corresponding 95 % confidence interval (CI).

3. Results

3.1. Demographic characteristics of the studied populations

The demographic characteristics of the studied populations were divided into four groups according to the sampling year (Table S3). Except for the degree of passive smoking ($p < 0.01$), significant differences were not observed in gender, age, BMI, maternal education level, or maternal occupation between different sampling years in children. However, the effect of passive smoking on urinary pollutant exposure and oxidative stress levels in children was negligible (Table S4). Significant differences were not observed in age, BMI, or smoking status in adults between the different sampling years, although such differences were observed for sex, with the number of female residents gradually increasing during the four-year sampling period ($p < 0.01$). Further difference analysis revealed that sex was an essential factor affecting the pollutant exposure levels of adults (Table S5). As children had more similar lifestyles and less demographic heterogeneity than adults, children were more suitable for longitudinal comparisons.

3.2. Heavy metal, PAH and VOC exposure and oxidative stress levels in adults and children

As shown in Table 1, the geomean concentrations of urinary MDA and 8-OHdG in children were approximately 1.55 and 1.67 times higher than those in adults, respectively ($p < 0.01$). The urinary MU, 2-OHN, and Mo were the most abundant VOC, PAH, and heavy metal in all studied populations (i.e., children and adults), respectively. Compared with adults, children had significantly higher levels of urinary MU, 1,2-DB, BMA, Cr, Mn, Co, Ni, Cu, Mo, Sn, Ba, and Pb ($p < 0.05$ or 0.01). In contrast, adults had significantly higher urinary PMA, 2-OHN, 1-OHN, 2-&3-OHF, 2-OHPhe, and Cd levels than children ($p < 0.01$). Overall, children had higher heavy metal and VOC exposure but lower PAH exposure than adults, indicating a significant difference in pollutant exposure profiles between children and adults. In addition, the Spearman correlation analysis showed that the levels of urinary MDA, 8-OHdG, MU, BMA, 2-OHN, 1-OHN, 2-&3-OHF, 3-OHPhe, 1-&9-OHPhe, 4-OHPhe, 1-OHP, Co, Ni, Cu, Mo, Sn, and Pb were significantly and negatively associated with age in children ($p < 0.05$ or 0.01) (Fig. S1), suggesting that younger children have higher levels of pollutant exposure and oxidative stress. Compared with children, the exposure of adults to heavy metals, PAHs, and VOCs had a weaker correlation with age, except for Cd (Fig. S1).

3.3. Associations of heavy metal, PAH, and VOC exposure with oxidative stress levels

The association between pollutant exposure and oxidative stress was evaluated through multiple linear regression. Greater β values suggest a higher oxidative damage potential of the chemicals. As shown in Fig. 1A, the urinary Cu, Mo, Cd, 2-OHN, 3-OHPhe, 1-&9-OHPhe, 1-OHP, MU, 1,2-DB, and BMA were significantly associated with the levels of 8-OHdG and MDA in urine. Cu, followed by BMA, Mo, 2-OHN, and 1-OHP, presented the top five associations with 8-OHdG levels, with β values ranging from 0.155 to 0.174. BMA, followed by Mo, Cu, Ni and Co, demonstrated the greatest association with MDA levels, with β values ranging from 0.121 to 0.211. In addition, the total β value of 8-OHdG was slightly higher than that of MDA (1.95 vs. 1.65) (Fig. 1B), suggesting that 8-OHdG is a more sensitive biomarker of oxidative stress than MDA.

3.4. Temporal trends in pollutant exposure and oxidative stress levels after e-waste control

The levels of urinary 2-&3-OHF, 2-OHPhe, 3-OHPhe, 1-&9-OHPhe, 4-OHPhe, 1-OHP, MU, and PMA in adults (Fig. 2A) and children (Fig. 2B) decreased significantly after e-waste control ($p < 0.01$), indicating that e-waste control effectively reduces human exposure to PAHs and VOCs.

Table 1
The levels of urinary pollutants and oxidative stress in children and adults in an e-waste recycling area located in southern China (μg/g CRE).

Analytes	Children (N = 275)					Adults (N = 485)					p-Values
	GM	P_{25th}	Median	P_{75th}	P_{95th}	GM	P_{25th}	Median	P_{75th}	P_{95th}	
MDA	314	242	322	423	625	202	158	199	262	428	0.000
8-OHdG	8.45	6.34	8.61	11.2	19.3	5.06	3.62	4.98	6.83	12.3	0.000
MU	61.6	28.4	71.2	130	411	37.9	19.6	39.0	73.7	182	0.000
1,2-DB	7.39	2.83	2.83	16.0	92.2	5.36	2.83	2.83	8.72	48.5	0.002
PMA	0.124	0.0710	0.0710	0.213	0.669	0.156	0.0710	0.109	0.296	0.987	0.000
BMA	5.35	3.32	5.11	8.61	22.3	3.89	2.37	3.78	6.38	14.5	0.000
2-OHN	3.77	2.36	3.56	5.78	14.0	4.91	2.34	4.25	11.1	25.4	0.002
1-OHN	2.89	1.80	3.48	6.18	20.9	3.87	1.87	3.96	8.56	22.9	0.029
2-&3-OHF	0.456	0.306	0.571	0.896	2.36	0.901	0.448	0.792	2.14	5.42	0.000
2-OHPhe	0.0435	0.0140	0.0480	0.100	0.265	0.0752	0.0423	0.0825	0.142	0.327	0.000
3-OHPhe	0.118	0.0800	0.136	0.210	0.598	0.121	0.0663	0.121	0.227	0.552	0.466
1-&9-OHPhe	0.203	0.118	0.250	0.458	1.01	0.246	0.147	0.266	0.448	1.02	0.254
4-OHPhe	0.0811	0.0210	0.0970	0.201	0.572	0.0672	0.0340	0.0750	0.134	0.322	0.018
1-OHP	0.195	0.128	0.199	0.320	0.653	0.193	0.119	0.185	0.331	0.663	0.629
Cr	3.57	1.23	3.08	7.67	53.6	3.69	1.23	2.70	10.4	42.3	0.655
Mn	3.01	1.29	2.48	4.53	43.0	2.15	1.25	1.80	2.93	8.98	0.000
Co	0.598	0.348	0.590	1.05	3.23	0.332	0.149	0.263	0.780	2.16	0.000
Ni	6.34	2.65	6.54	11.9	35.8	4.21	2.11	3.89	7.30	19.1	0.000
Cu	17.4	10.9	16.4	26.8	87.0	11.8	7.92	11.0	18.1	37.6	0.000
Mo	131	83.1	136	203	347	54.5	37.7	54.0	80.4	151	0.000
Cd	0.348	0.227	0.454	0.695	1.41	0.828	0.495	0.840	1.60	3.13	0.000
Sn	3.50	1.64	3.11	8.08	31.5	2.20	1.11	2.05	4.02	11.2	0.000
Ba	5.83	2.91	3.44	9.81	65.1	4.09	2.79	3.17	4.63	17.3	0.001
Pb	5.23	1.55	4.69	15.4	74.2	3.56	1.65	3.50	6.91	25.0	0.008

Differences in the levels of urinary analytes between children and adults were examined using a Mann-Whitney U test.
Abbreviations: GM, geomean; P, percentile; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; MDA, malonaldehyde; MU, *trans*,*trans*-muconic acid; 1,2-DB, 1,2-dihydroxybenzene; PMA, *s*-phenylmercapturic acid; BMA, *s*-benzylmercapturic acid; 2-OHN, 2-hydroxynaphthalene; 1-OHN, 1-hydroxynaphthalene; 2-&3-OHF, 2-&3-hydroxyfluorene; 1-&9-OHPhe, 1-&9-hydroxyphenanthrene; 2-OHPhe, 2-hydroxyphenanthrene; 3-OHPhe, 3-hydroxyphenanthrene; 4-OHPhe, 4-hydroxyphenanthrene; 1-OHP, 1-hydroxypyrene; Cr, chromium; Mn, manganese; Co, cobalt; Ni, nickel; Cu, copper; Mo, molybdenum; Cd, cadmium; Sn, tin; Ba, barium; Pb, lead.

However, the declining trend of heavy metal exposure levels in the population is not as obvious as that of PAHs and VOCs. Among the ten heavy metals, only the urinary Sn level in children and adults decreased significantly over time ($p < 0.01$); moreover, the urinary Cd level in adults increased significantly over time ($p < 0.01$). Overall, from 2016 to 2019, the urinary Sn and PMA showed the most dramatic decreases among the

A

Rank	8-OHdG		MDA	
	Compounds	β (95% CIs)	Compounds	β (95% CIs)
1	Cu	0.174 (0.125, 0.223)	BMA	0.211 (0.170, 0.252)
2	BMA	0.172 (0.127, 0.216)	Mo	0.188 (0.136, 0.241)
3	Mo	0.165 (0.109, 0.221)	Cu	0.167 (0.121, 0.213)
4	2-OHN	0.155 (0.116, 0.195)	Ni	0.160 (0.119, 0.201)
5	1-OHP	0.155 (0.109, 0.200)	Co	0.121 (0.084, 0.159)
6	4-OHPhe	0.130 (0.098, 0.162)	MU	0.109 (0.078, 0.139)
7	Ba	0.107 (0.051, 0.162)	1-OHP	0.108 (0.064, 0.151)
8	1-OHN	0.106 (0.077, 0.135)	PMA	0.075 (0.035, 0.114)
9	1-&9-OHPhe	0.095 (0.060, 0.129)	1, 2-DB	0.073 (0.043, 0.103)
10	1, 2-DB	0.091 (0.060, 0.122)	2-OHN	0.055 (0.016, 0.094)
11	3-OHPhe	0.090 (0.052, 0.127)	Cd	0.050 (0.010, 0.089)
12	Sn	0.084 (0.049, 0.120)	3-OHPhe	0.049 (0.013, 0.085)
13	Pb	0.075 (0.038, 0.111)	1-&9-OHPhe	0.049 (0.016, 0.082)
14	2-&3-OHF	0.070 (0.036, 0.104)	Ba	0.044 (-0.010, 0.098)
15	Cd	0.058 (0.016, 0.100)	Pb	0.031 (-0.002, 0.064)
16	MU	0.050 (0.017, 0.083)	Cr	0.029 (0.001, 0.056)
17	Ni	0.044 (-0.001, 0.088)	Mn	0.027 (-0.014, 0.068)
18	2-OHPhe	0.040 (0.003, 0.078)	2-&3-OHF	0.025 (-0.008, 0.058)
19	PMA	0.022 (-0.019, 0.064)	1-OHN	0.016 (-0.012, 0.044)
20	Mn	0.020 (-0.023, 0.064)	Sn	0.016 (-0.018, 0.049)
21	Co	0.002 (-0.039, 0.042)	4-OHPhe	0.014 (-0.018, 0.045)
22	Cr	-0.022 (-0.052, 0.007)	2-OHPhe	0.011 (-0.025, 0.046)

B

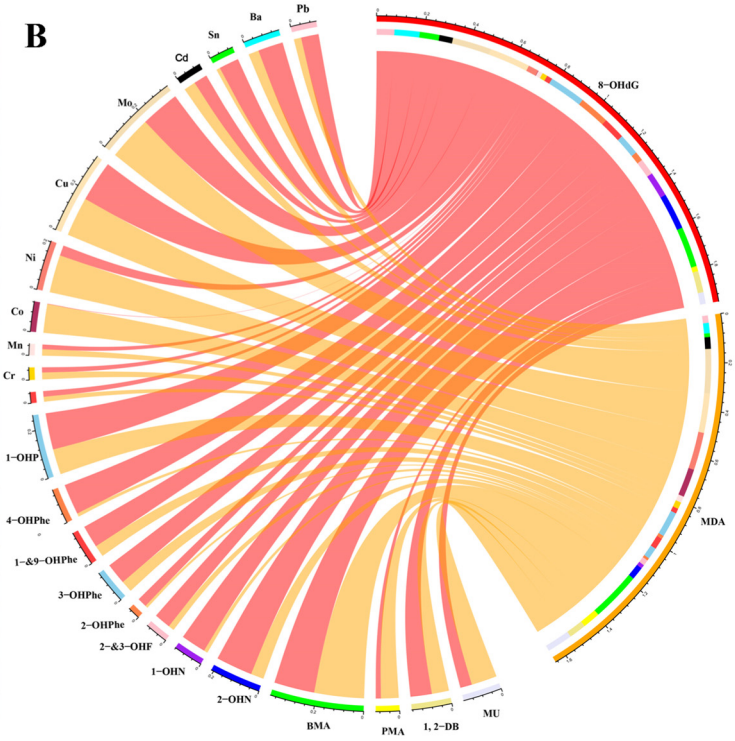

Fig. 1. Association of heavy metal, PAH and VOC exposure with oxidative stress levels. Multiple linear regression with adjustment for age, gender, BMI and sampling year was employed. Fig. 1A: The strength of their relationship is expressed by regression coefficients (β) and their corresponding 95 % CIs. Fig. 1B: Chord diagram. The width of the lines is proportional to the β values. For each chemical segment (color rectangular bands on the left semicircle), the arc length represents the total effects of oxidative stress. For each oxidative damage indicator segment (colored rectangular bands on the right semicircle), the arc length represents the total effects induced by pollutant exposure.

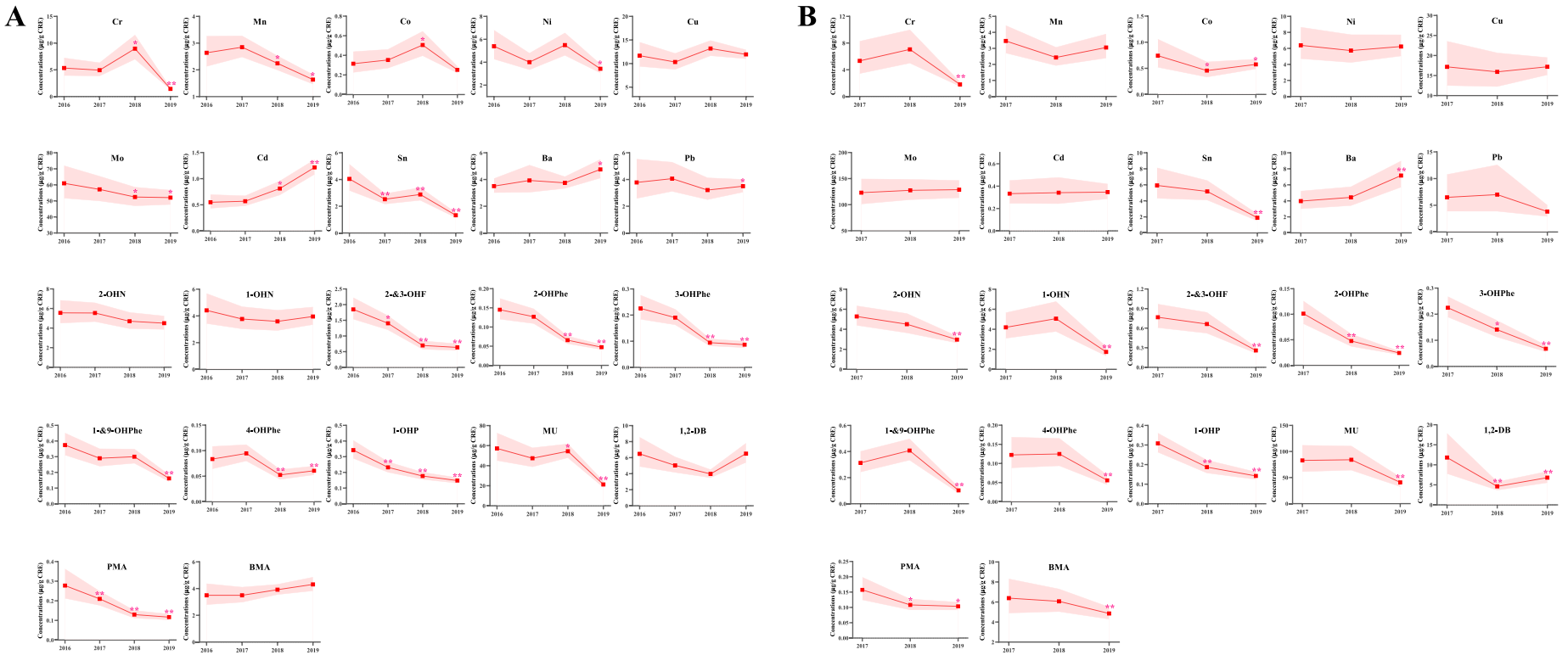

Fig. 2. Temporal trends of exposure levels of heavy metals, PAHs and VOCs in adults (A) and children (B) from 2016 to 2019 after e-waste control. The data were shown as geomean concentrations and corresponding 95 % confidence intervals (CIs). The sample sizes of adults from 2016 to 2019 were 67, 107, 135 and 176, respectively. The sample sizes of children from 2016 to 2019 were 25, 61, 65 and 124, respectively. The levels of pollutant exposure in 2017, 2018 and 2019 were compared to those in 2016 using a one-way analysis of variance test. Due to the small sample size for children in 2016, the levels of pollutant exposure in 2018 and 2019 were compared to those in 2017 rather than in 2016 using one-way analysis of variance. $^{*}p < 0.05$, $^{**}p < 0.01$.

heavy metals and VOCs, respectively (Fig. S2). For PAHs, the levels of 2-&3-OHF, 3-OHPhe, and 1-OHP in the urine of children and adults exhibited a similar dramatically monotonous downward trend (Fig. S2). Compared with 2016, the geomean levels of urinary Sn, PMA, 2-&3-OHF, 3-OHPhe, and 1-OHP in all recruited populations in 2019 decreased significantly by 69.3 %, 58.1 %, 71.1 %, 66.3 % and 57.9 %, respectively (Fig. S2). Furthermore, the decline in pollutant exposure in children was more obvious than that in adults (Fig. S2). Interestingly, although the urinary MDA concentration in children did not decline over time, the urinary 8-OHdG level decreased significantly by 17.6 %, from 9.45 μg/g CRE in 2017 to 7.79 μg/g CRE in 2019 ($p < 0.01$) (Fig. 3). Therefore, implementing e-waste control measures effectively reduces the human risk of oxidative stress from e-waste dismantling activities.

3.5. Potential biomarkers of e-waste pollution

As noted above, the urinary Sn, PMA, 2-&3-OHF, 3-OHPhe, and 1-OHP levels decreased monotonically and dramatically after e-waste control; thus, they may be potential exposure biomarkers of e-waste pollution. The exposure levels of all populations (i.e., children and adults) in this study were further compared with the general populations in the United States (USA) and Canada (CDC, 2021; HC, 2015). As shown in Table S6, the geomean concentrations of urinary Sn, 2-&3-OHF, 3-OHPhe, and 1-OHP in this study population were 8.97, 5.03, 3.30, and 2.26 times higher than those in the USA, respectively. The geomean concentrations of urinary 2-&3-OHF, 3-OHPhe, 1-OHP, and PMA in this study population were 4.11, 2.71, 3.68, and 1.47 times higher than those in Canada, respectively. Furthermore, the concentration ratios of the above biomarkers in this study population were distinctly different from those in other study populations (Fig. S3). For example, the concentration ratios of urinary Sn/1-OHP and 2-&3-OHF/PMA in this study population were 3.97 (ratio: 14.4 vs. 3.63) and 2.79 (ratio: 5.74 vs. 2.06) times higher than those in the USA and Canada, respectively. Hence, the exposure levels of Sn, PMA, 2-&3-OHF, 3-OHPhe, and 1-OHP and their corresponding concentration ratios may be useful biomarkers to indicate e-waste pollution.

In addition, urine samples from different years were visually classified using the concentrations of urinary Sn, PMA, 2-&3-OHF, 3-OHPhe, and 1-OHP (Fig. 4) as biomarkers. The classification effects of e-waste pollution in different years were similar when using urinary Sn and PMA in combination with 1-OHP (Fig. 4A), 2-&3-OHF (Fig. 4B), or 3-OHPhe (Fig. 4C) as biomarkers. Compared with 2016, the overlap of the 95 % confidence ellipsoids gradually decreased with time, suggesting that these exposure biomarkers in urine are helpful for distinguishing the degree of exposure to e-waste pollution. However, we found that the use of urinary PAHs alone as exposure biomarkers (i.e., 2-&3-OHF, 3-OHPhe, and 1-OHP) (Fig. S4) or a combination of exposure and effect biomarkers (e.g., Sn, 1-OHP, and 8-OHdG) (Fig. S5) did not achieve a good classification result.

4. Discussion

4.1. E-waste control effectively reduces environmental pollution and human exposure risk

One objective of this study is to evaluate the effectiveness of the regulations on informal e-waste recycling activities. Informal e-waste recycling releases many toxic substances, including heavy metals and persistent organic pollutants (Ahirwar and Tripathi, 2021). After e-waste control, a significant decline in organic pollutant exposure (i.e., naphthalene, fluorene, phenanthrene, pyrene, benzene, and toluene) was observed in the studied populations, especially children. Before 2012, biomonitoring studies were also conducted in this e-waste recycling area. In our study, the levels of urinary 2-&3-OHF and 1-OHP in adults in 2019 were approximately 4.0 and 7.0 times lower than the previous levels, respectively (Table S7) (Huo et al., 2019; Wang et al., 2014). After e-waste control, the PAH level in the urine of local children dropped to a level close to that of children in uncontaminated areas (Table S7) (CDC, 2021; Kuang et al., 2020). As the e-waste dismantling process accounts for approximately 20 % to 80 % of atmospheric PAHs and VOCs (Chen et al., 2021; Chen et al., 2019), strict e-waste control measures will undoubtedly contribute to the effective reduction of human exposure to organic pollutants. Recently, Tang et al. also reported a declining trend in the hair levels of polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs) and organophosphorus flame retardants (OPFRs) in local residents and workers after the implementation of legislation and regulations on informal e-waste recycling activities (Tang et al., 2022). Based on the significant positive association between PAH/VOC exposure and 8-OHdG, the apparent decrease in PAH/VOC exposure levels in children may partly account for the significant decrease in oxidative DNA damage levels.

Heavy metal pollution is inevitable during informal e-waste recycling activities (Ahirwar and Tripathi, 2021). One unanticipated finding was that the variation in human exposure to heavy metals was different from that to organic pollutants after e-waste control. Except for Cr and Sn, the urinary levels of other heavy metals (e.g., Cd) remained unchanged or increased significantly over time. The population exposure levels of heavy metals in 2019 were still distinctly higher than those in other reference areas. For example, the geomean levels of urinary Mn, Ni, Cu, and Pb in

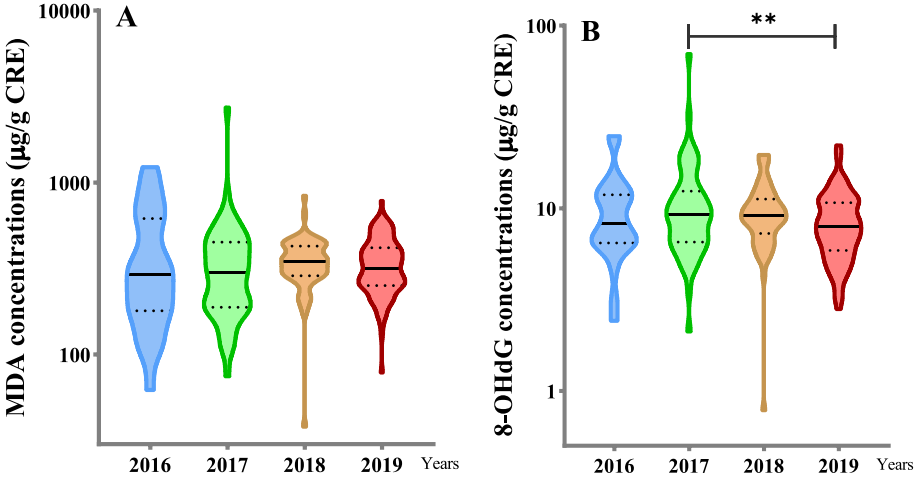

Fig. 3. Variations in urinary concentrations of MDA (A) and 8-OHdG (B) in children from 2016 to 2019. Any differences between groups were examined using one-way analysis of variance. $^{**}p < 0.01$. The solid line and dotted lines represent the median and quartiles of MDA or 8-OHdG concentrations, respectively.

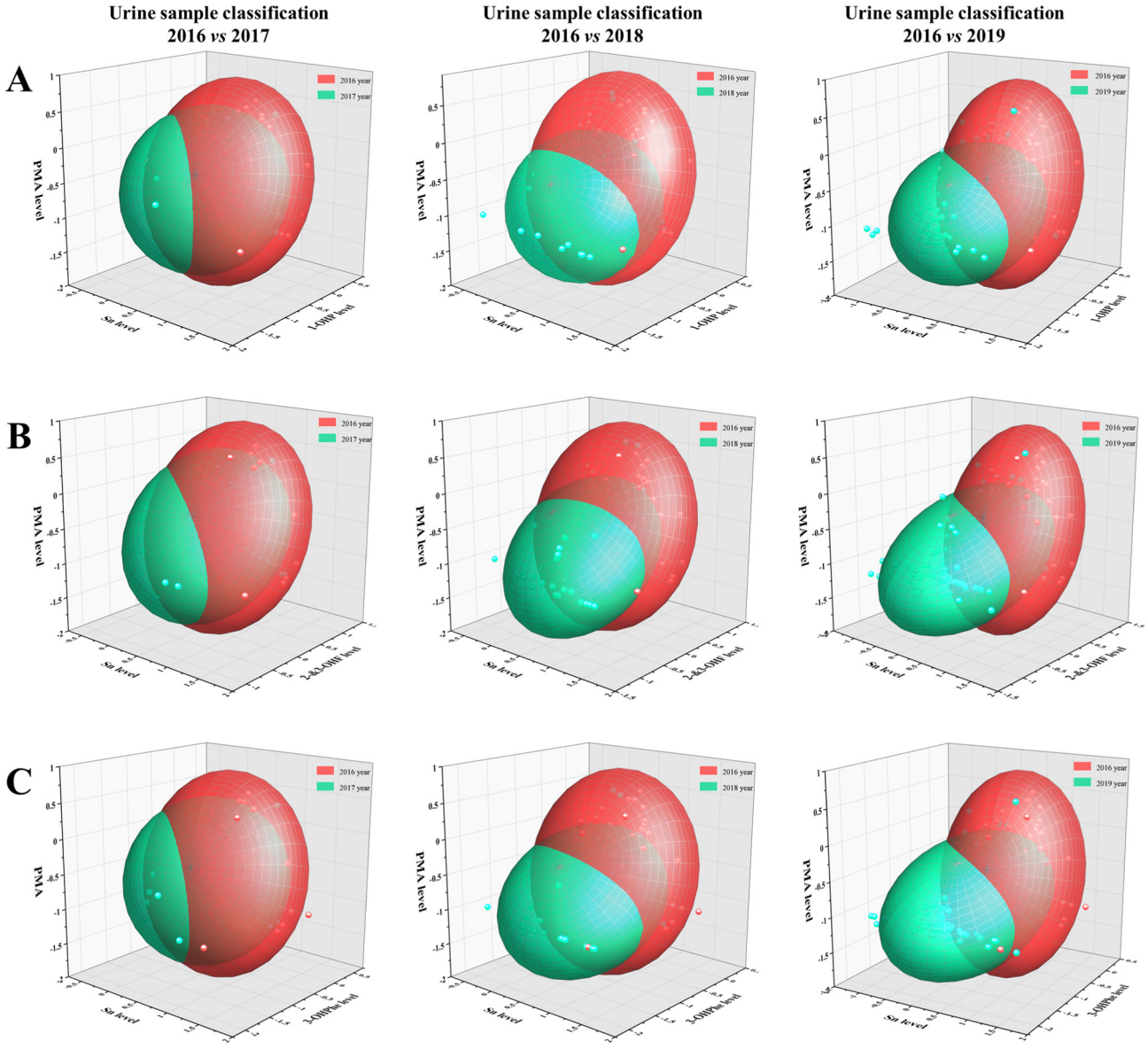

Fig. 4. Visual classification of urine samples from different years using potential biomarkers of e-waste pollution. The spherules represent the three-dimensional spatial distribution of concentrations of e-waste biomarkers. Based on the distribution characteristics of spherules, their corresponding 95 % confidence ellipsoids were fitted. The lower the overlap of the two 95 % confidence ellipsoids, the better the classification effect. The red spherules and 95 % confidence ellipsoids represent the spatial distribution of urine samples in 2016, while the green ones represent urine samples in 2017, 2018 or 2019. Fig. 4A shows the classification of urine samples from different years using urinary Sn, PMA and 1-OHP as biomarkers. Fig. 4B shows the classification of urine samples from different years using urinary Sn, PMA and 2-&3-OHF as biomarkers. Fig. 4C shows the classification of urine samples from different years using urinary Sn, PMA and 3-OHPhe as biomarkers.

children in this study were approximately 2.3–24, 2.1–3.0, 1.6–1.8, and 2.6–12 times higher than those in China and the USA, respectively (Table S8) (CDC, 2021; Li et al., 2020; Xue et al., 2020), while the geomean levels of urinary Cd, Sn, Ba, and Pb in adults in this study were approximately 6.7, 2.8, 3.9, and 10 times higher than those in the USA, respectively (Table S8). In addition, heavy metal exposure (e.g., Cu, Mo and Ni) had a stronger correlation with MDA levels than organic pollutant exposure, except for BMA (Fig. 1). Continued exposure to high levels of heavy metals may be the reason why the MDA levels in the population did not decline despite four years of e-waste control. The high levels of heavy metal exposure in the populations after e-waste control have several possible explanations. On the one hand, the informal recycling of e-waste over the past 40 years has led to severe environmental pollution. High levels of heavy metals were observed in soils or sediments of this e-waste recycling area, with the Cr, Cu, and Pb reaching values that were 2.4, 2.6, and 17 times higher than those in agricultural soil of the reference area, respectively (Table S9) (Nie et al., 2015; Xiao et al., 2020; Yekeen et al., 2016; Zhao et al., 2015). As heavy metals are generally difficult to degrade, higher environmental heavy metals will increase the corresponding burden of human exposure. On the other hand, the bioaccumulation of heavy metals also accounts for their high levels in the human body. For example, Cd primarily accumulates in the kidneys and liver and has an estimated half-life of 4 to 38 years (Young and Cai, 2020). Urine and blood Cd levels are the most specific biomarkers of Cd exposure (Klotz et al., 2013), with blood Cd levels reflecting recent exposure and urinary Cd levels indicating long-term cumulative exposure (Klotz et al., 2013). Our findings revealed that urinary Cd levels in children and adults were positively associated with age, suggesting the bioaccumulation of Cd in the local population. Hence, early exposure to high levels of heavy metals that present high bioaccumulation may lead to high levels of heavy metals in the urine, even after e-waste control.

Taken together, the implementation of e-waste control measures facilitates the effective reduction of human exposure to various pollutants and oxidative DNA damage risk. These achievements were attributed to the implementation of 10 hallmark e-waste control measures since 2015 (MEE, 2019), including the formulation of relevant laws and regulations, increases in public awareness of environmental protection, acceleration of industrial upgrading and transformation, elimination of primitive or rough e-waste dismantling activities, establishment of an environmental pollution reporting system, promotion of the transformation from the individual operation into collective operation and enterprise operation, construction of a full-chain e-waste dismantling industrial park, and strengthening of environmental infrastructure construction and environmental restoration (Text S5).

4.2. Biomarkers of e-waste pollution

In this study, the levels of urinary Sn, PMA, 2-&3-OHF, 3-OHPhe, and 1-OHP, which are indicators of exposure to Sn, benzene, fluorene, phenanthrene, and pyrene, respectively, decreased significantly and monotonically after e-waste control. Sn is an essential component of printed circuit boards and accounts for >4.6 % of their total mass (Pokhrel et al., 2020). The recovery process of Sn from a printed circuit board includes high-temperature dissolution and refining (Pokhrel et al., 2020), in which Sn is easily volatilized into the atmosphere due to its low melting point. Informal e-waste recycling results in large amounts of Sn being released into the environment (Quan et al., 2015), making it the second most toxic metal to the human body (Pokhrel et al., 2020). Different from Sn, benzene, fluorene, phenanthrene and pyrene are byproducts of e-waste that are inevitably produced during e-waste incineration (Ahirwar and Tripathi, 2021; Liu et al., 2017). In this study, the levels of urinary Sn, PMA, 2-&3-OHF, 3-OHPhe, and 1-OHP in 2016 were approximately 1.47 to 8.97 times higher than those in the USA and Canada (CDC, 2021; HC, 2015). The combination of urinary Sn and PMA with 1-OHP, 2-&3-OHF or 3-OHPhe as biomarkers demonstrates good and similar effects in distinguishing e-waste pollution and indicates the effectiveness of the control measures, suggesting that the biomonitoring of these urinary biomarkers facilitates evaluations of the degree of e-waste pollution. However, the classification effect is greatly reduced if only urinary PAHs are used as biomarkers (i.e., 2-&3-OHF, 3-OHPhe and 1-OHP), which may be related to the more comprehensive prediction of e-waste pollution profiles when using multiple categories of pollutants (i.e., heavy metals, PAHs and VOCs) as indicators compared with using one. Notably, the concentration ratios of these biomarkers in this study were distinctly different from those in other populations (Fig. S3), which suggests that the concentration ratios, such as the ratio of Sn to 1-OHP, are also potentially valuable indicators of e-waste pollution.

In addition to exposure biomarkers, effect biomarkers associated with pollutant exposure are increasingly used in toxicity and risk assessment (Sun et al., 2022). 8-OHdG and MDA have been extensively used as effect biomarkers after exposure to typical pollutants (Mukherjee and Agrawal, 2017). In this study, 19 out of 24 pollutants in urine were significantly and positively associated with 8-OHdG (Fig. 1). Moreover, the 8-OHdG level demonstrated a significant declining trend after e-waste control, suggesting that 8-OHdG in urine may be a potential effect biomarker of e-waste pollution. However, using 8-OHdG as a biomarker could not distinguish e-waste exposure levels among populations in different years (Fig. S5), which may be because the decline in the 8-OHdG level was not as significant as that of Sn and 1-OHP.

4.3. Children are vulnerable to e-waste pollution

In this study, children were generally exposed to higher levels of heavy metals and VOCs and suffered a higher risk of oxidative DNA and lipid stress than adults under the same exposure conditions (i.e., exposure time and location) (Table 1). Interestingly, we found that age was an important factor related to children's susceptibility. Younger children had higher burdens of pollutant exposure and oxidative stress, whereas this was not observed in adults (Fig. S1). Another population study reported a similar finding. For example, exposure to PAHs and VOCs in a coal industry region of northern China significantly impaired children's lung function but not adults' (Chen et al., 2018). These phenomena may be explained by the following reasons. First, the toxic dynamic processes that determine human exposure, absorption, metabolism, excretion and tissue vulnerability are age-related (Bearer, 1995). Because the air and food intake per unit of body weight are higher in children than adults, the pollutant intake in children is higher than in adults because of their relative size differences. In addition, children present incomplete metabolism and elimination systems, rapid tissue regeneration and immature host defenses, which make them more susceptible and vulnerable to environmental pollutants (Heacock et al., 2016) because children's bodies cannot break down and eliminate harmful substances (WHO, 2021). Second, hand-to-mouth behavior in children increases their risk of ingesting contaminants. Evidence has shown that prenatal or childhood e-waste exposure is significantly associated with impaired neurodevelopment and behavior, negative birth outcomes, impaired thyroid function and immune system functions, and increased DNA damage (Parvez et al., 2021). Inconsistently, we observed that adults were exposed to higher PAH levels than children. In addition to sources from informal e-waste recycling, individual PAH exposure can be affected by other environmental sources or lifestyles, such as cigarette smoking and cooking (Cao et al., 2020). Adults are generally responsible for cooking at home. Moreover, male adults who smoked accounted for 35.1 % of the total adult population in this study. These adult-specific behaviors may lead to their higher levels of PAH exposure than children.

To our knowledge, this is the first longitudinal population exposure study to investigate the impact of e-waste control on human pollutant exposure and oxidative stress. We found that human levels of oxidative DNA damage and exposure to PAHs, VOCs and some heavy metals decreased significantly after e-waste control, which provides evidence for the effectiveness of regulations on informal e-waste recycling activities in China. Moreover, several urinary pollutants were identified as potential biomarkers of e-waste pollution based on the temporal trends of human exposure levels after e-waste control. However, whether our findings can be applied to other e-waste recycling sites must be confirmed due to the variabilities in the types and quantities of e-waste, the length of the e-waste recycling history, and the methods and locations of disposal activities. The conclusions will be more convincing if they are obtained from a cohort study. However, as long as the sampling population is representative and the sampling sizes achieve sufficient statistical power, the results can reflect the impact of e-waste pollution on population exposure, regardless of whether cohort studies are used. Another limitation of this study cannot be ignored: based on the simplicity of sampling and pretreatment, urine samples were used to reflect the human pollutant profile; thus, certain lipid-soluble e-waste pollutants commonly found in blood and hair, such as PBDE, PCB, and OPFRs, were not monitored (Lin et al., 2020; Tang et al., 2022).

5. Conclusions

Implementing e-waste control measures effectively reduces human exposure to PAHs, VOCs and certain heavy metals as well as the risk of oxidative DNA damage. The combination of urinary Sn and PMA with 1-OHP, 2-&3-OHF or 3-OHPhe as biomarkers demonstrated a good classification effect on e-waste pollution and control. These biomarkers are helpful for assessing the effectiveness of the government's pollution regulation and policy measures. However, the levels of oxidative lipid stress damage levels and most heavy metals in urine remained unchanged despite four years of e-waste control, suggesting the long-lasting and profound impacts of e-waste pollution on human health. In addition, as children are more vulnerable to e-waste pollution than adults, urgent global action is needed to protect millions of children from e-waste pollution. This work has tremendous economic and social value because it provides a reference for

formulating environmental management and public health protection policies for e-waste recycling sites.

CRediT authorship contribution statement

Hongxuan Kuang: Writing - original draft, Formal analysis, Investigation, Methodology. **Yonghong Li**, **Leizi Li**, **Shengtao Ma**: Investigation. **Ruifang Fan** and **Taicheng An**: Supervision; Review of experimental scheme & protocol; Writing - review & editing.

Declaration of competing interest

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

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Appendix A. Supplementary data

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