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Exposure to polycyclic aromatic hydrocarbons (PAHs) in outdoor air and respiratory health, inflammation and oxidative stress biomarkers: A panel study in healthy young adults

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ABSTRACT

Exposure to polycyclic aromatic hydrocarbons (PAHs) can be associated with different types of health effects. However, the systemic changes of health effects between fluctuations of PAHs exposure have not been established. In this study, urinary hydroxylated PAHs (OH-PAHs) and 12 biomarkers were determined among 36 students from the urban to the suburb in Taiyuan in 2019. The concentration of Σ_{12}OH-PAHs in urban areas (28.2 and 21.4 μg/g Cr) was significantly higher than that in suburban area (16.8 μg/g Cr). The regression showed that hydroxy-phenanthrene (OH-Phe, 1/2/3/4/9-OH-Phe) was significantly positively correlated with lung function (PEF_{25} and PEF_{50}), 8-hydroxydeoxyguanosine (8-OHdG), interleukin-8 (IL-8), and fractional exhaled nitric oxide (FeNO). Moreover, there were negative associations of 2-hydroxyfluorene (2-OH-Flu) with FVC and FEV_1. 1 unit increase of 1-hydroxypyrene (1-OH-Pyr) was negatively associated with 18.8% FVC, 17.3% FEV_1, and 26.4% PEF_{25} in the suburban location, respectively. During $urban_2$, each unit change of 2-OH-Flu was associated with 10.9% FVC and 10.5% FEV_1 decrease, which were higher than those in suburban location. 8-OHdG decreased by 32.0% with each unit increase in 3-hydroxyfluorene (3-OH-Flu) during $urban_2$ ($p < 0.05$), while 1.9% in the suburban location. During the suburban period, the increase in OH-Phe was correlated with the decrease in malondialdehyde (MDA). The respiratory damage caused by PAHs in the urban disappeared after backing to the urban from the suburban area. Notably, despite the total significant liner mixed regression association of FeNO with multiple OH-PAHs, the association of FeNO with OH-PAHs was not significant during different periods except for 2-OH-Flu. Our findings suggested that short-term exposure to different concentrations of PAHs might cause changes in health effects and called for further research to investigate possible alterations between health effects and PAH exposure.

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) attracted increasing attention due to their extensive environmental distribution and deleterious effects on humans. Anthropogenic emissions, including process manufacturing, tailpipe, domestic, and agricultural sources, were the important determinants of PAHs pollution (Mallah et al., 2022). High concentrations of PAHs in air, soil, and water have been reported in scientific articles (Alegbeleye et al., 2017; Kim et al., 2013). Moreover, accumulation of PAHs has been demonstrated at occupational exposure (Lin et al., 2020; Ma et al., 2021; Meng et al., 2022) and in the general population (Huang et al., 2022; Zhang and Li, 2023), resulting in an

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elevated risk of adverse health effects.

Inhalation and diet intake are the prevalent routes of human contamination with PAHs. In addition, many studies have linked the effects of PAH external exposure to allergies and respiratory and cardiovascular diseases (Campisi et al., 2023; Wang et al., 2012; Yu et al., 2015). However, external exposure assessment to PAHs might be misjudged due to the partial bioavailability of PAHs (Zhu et al., 2019). As metabolites of PAHs, hydroxylated polycyclic aromatic hydrocarbons (OH-PAHs) generally have short half-lives, providing vital information on recent PAHs exposure from various sources and pathways (Li et al., 2010). Moreover, urinary OH-PAHs have been measured in a series of surveys for internal exposure assessment (Huang et al., 2022; Li et al., 2021; Yao et al., 2019; Yu et al., 2021; Zhou et al., 2018a).

PAHs have been demonstrated to link inflammation-related diseases, such as asthma (Rosa et al., 2011), deteriorated lung functions (Zhou et al., 2018b), chronic obstructive pulmonary disease (Kazmierczak et al., 2015), and ischemic stroke (Tanaka et al., 2023), which is suggestive evidence of PAHs indicating proinflammatory effects on airways. Although there are still some ambiguous points in the mechanism, previous studies have investigated that inflammatory indices like serum C-reactive protein, interleukin-8 (IL-8), and IL-10 are all associated with PAHs exposure (Everett et al., 2010; Farzan et al., 2016; Ferguson et al., 2017). However, these biomarkers reflect systemic inflammation other than specific markers of the airway and lung. Fractional exhaled nitric oxide (FeNO) originating from the airway cell was widely used to assess airway inflammation (Zhang et al., 2022b). Remarkably, increasing numbers of epidemiological studies, mostly with cohort designs, have associated PAHs exposure with FeNO (Li et al., 2019; Zhang et al., 2022a), suggesting a critical component of inflammation in the process of PAHs affecting health. Furthermore, the intensity of the action of OH-PAHs on characterizations of lung function may be inconsistent owing to different environmental distributions (Agudelo-Castaneda et al., 2017). However, concrete evidence is lacking as comprehensive relationships of impaired respiratory system with inflammations and oxidative damage induced by PAHs exposure cessation. As shown in previous publications (Lin et al., 2022; Lin et al., 2016; Lu et al., 2021), repeated measurements of travelers offer a great potential for the effects of exposure while reducing the fluctuation contributed by individual factors. Thus, verifying the association between OH-PAHs and multiple respiratory biomarkers is essential to explore the mechanism of respiratory injury.

Taiyuan is one of the Chinese industrial cities, and the lifestyle and development situation are representative of most northern cities in China (Song et al., 2020; Yan et al., 2017). Combined with geographical structure, the estimated lung cancer prevalence owing to PAHs exposure indicates the importance of reducing PAHs (Duan et al., 2014). Therefore, a panel experiment was conducted on healthy young adults to explore the health effects of PAHs exposure. The experiment is designed for (1) examining the OH-PAHs levels during different exposure periods; (2) estimating associations between OH-PAHs and respiratory health, including lung function and FeNO; (3) comparing associations between OH-PAHs and inflammation factors and oxidative stress. To our knowledge, this is one of the few studies on associations between PAHs, FeNO, lung function, and other inflammatory biomarkers among healthy young adults in Northern China.

2. Materials and methods

2.1. Study design and exposure assessment

A panel experiment during the high-low exposure exchange program was conducted. Thirty-six healthy students (17 males and 19 females) were recruited in Taiyuan from November to December 2019, averaging 23.4 ± 1.6 years. The body mass index was 21.7 ± 8.6 kg/m^2. None of the subjects were self-reported smokers or drinkers. All 108 first-morning urine samples acquired were stored in polypropylene tubes and frozen at −80 °C until analysis. Briefly, three paired peripheral samples were acquired prior to ($urban_1$), during (suburb), and past ($urban_2$) the panel program. All urine was obtained after fasting at least 8 h to avoid potential dietary impacts. The study protocol was registered at clinicaltrials.gov (ChiCTR2200066147) and was approved by the Ethics Committee of Shanxi University (SXULL2019070). All participants gave written informed consent.

$PM_{2.5}$ samples, lung function, airway inflammatory markers, systemic inflammatory markers, and oxidative stress markers were characterized based on the methods presented in the SI section.

2.2. Chemicals and reagents

The chemicals and reagents used in this study were described in SI.

2.3. Sample preparation and analysis

$PM_{2.5}$ was dissolved in a mixture of ether/hexane (10/90, v/v) and separated by column chromatography. Sixteen target PAHs (Table S1) were determined by gas chromatography and mass spectrometry (GC–MS, Agilent Technologies, Inc. USA).

The pretreatment of urine was based on our previously published studies (Huang et al., 2022; Yang et al., 2021). Briefly, after enzymatic hydrolysis of the sample and precipitation of the protein, twelve OH-PAHs were analyzed by liquid chromatography-tandem mass spectrometry under online extraction and purification. Detailed information about sample preparation and analysis was given in SI.

2.4. Quality assurance and quality control

All measurements of PAHs were performed in strict accordance with the national standard HJ646–2013. One blank procedure and one spiked sample were performed for each batch. The spiked recoveries of isotope-labelled PAHs were 71.5%–111.0%. All data were corrected for blank in this study. The detection limits were 0.02–0.04 ng/m^3 for PAHs (Table S1).

For OH-PAHs, a procedural blank, a reagent blank, and two matrix spikes were carried out for each of the 10 field samples. The recoveries were 55.6%–104.8% after calibration with internal standards. Reported concentrations were not surrogate recovery corrected. Creatinine was used to adjust OH-PAHs. The limits of quantification were 0.001–3.044 ng/mL for OH-PAHs (Table S2).

2.5. Statistical analysis

Mann−Whitney *U* test was used to assess the difference in OH-PAHs concentrations, lung function, FeNO, and serum biomarkers among different periods. Spearman's rank correlation test was applied to study correlations between OH-PAHs concentrations and health variables. Linear regression models were used to study associations between OH-PAHs concentrations and the health effects on different PAHs levels, adjusted for gender, age, and body mass index (Eq. (1)). A linear mixed-effects model was used to study relationships between OH-PAHs concentrations in all three exposure periods and health effect levels with the number of each person as a random effect to account for individual differences, adjusted by gender, age, and body mass index (Eq. (2)).

$$Y_{it} = \alpha + \beta X_{it} + \varepsilon_{it} \quad (1)$$

where Y_{it} means the log-transformed concentrations of FeNO, lung function, IL-8, MDA, and 8-OHdG in serum and X_{it} means OH-PAHs of subject i during t periods; α is the model fixed intercept; β represents the regression coefficient of the linear; ε_{it} is the residual;

$$Y_{it} = \alpha + \mu_i + \beta X_{it} + \varepsilon_{it} \quad (2)$$

β represents the linear mixed regression model coefficient, and μ_i is

the random intercept for subject i. The results were expressed as percent changes in respiratory health effects associated with a unit change in log-transformed OH-PAHs level as $(10\ \hat{}\ \beta - 1) \times 100\%$, with 95% confidence intervals (CIs). We performed a mediation analysis to assess the role of inflammation and oxidative stress biomarkers' potential effects of the association between PAHs exposure and respiratory health. A two-tailed $p < 0.05$ was considered significant.

2.6. Risk assessments

The exposure to atmospheric PAHs by inhalation was evaluated based on toxic equivalency factors (TEFs). Moreover, the carcinogenic risk of internal exposure (CR_i) was evaluated by urinary OH-PAHs. Details were listed in SI Table S3.

3. Results and discussion

3.1. External exposure and risk assessment of $PM_{2.5}$-bound PAHs

The total concentrations of $PM_{2.5}$-bound PAHs ($\sum_{16}$PAHs) in urban areas were 11.5 and 12.0 ng/m^3, respectively, which were higher than that in the suburb area (9.9 ng/m^3) (Fig. 1a). This was inconsistent with the previous report that the PAHs levels ranged from 24.2 to 3029 ng/m^3 and the exposure level of rural residents during the heating season was slightly higher than that of urban in 2009 (Duan et al., 2014). Previous studies demonstrated that PAHs concentrations were reduced by 97.5% and 88.1% in 2014–2015 (Yan et al., 2017) and 2017 (Zhang et al., 2019), respectively. Ratios of PAHs/$PM_{2.5}$ exhibited reductions of 81.9% in 2017 (Zhang et al., 2019). This confirmed that the substantial decrease in PAHs was more significant than that of $PM_{2.5}$, indicating that the pollution control measures for $PM_{2.5}$ positively contributed to reducing PAHs. However, now the concentration of $\sum_{16}$PAHs is still higher than the reported levels in Hong Kong (0.665 ng/m^3) (Fan et al., 2018) and Guangzhou (2.71 ng/m^3) (Zhang et al., 2021).

The composition profiles of PAHs in the exchange program followed similar patterns. Fluo and BbF were the most predominant congeners, accounting for 14.4%–16.0% and 17.0%–20.2% of the $\sum_{16}$PAHs in urban and suburb areas, respectively (Fig. 1b). The composition profiles in this work were consistent with the reports in 2017 (Zhang et al., 2019). However, these results differed from the composition distribution of PAHs in 2013 (Xia et al., 2013), where Phe (22.0%) is the most abundant element other than Fluo (25.5%), and the percentage of BbF is small (< 0.1%). This may be attributed to the fact that clean energy usage has changed the $PM_{2.5}$ composition and needs further study (Yan et al., 2017).

The median BaP_{eq} were 2.15, 1.76, and 1.85 ng/m^3 in $urban_1$, suburb, and $urban_2$, respectively (Fig. S1a). This value was lower than the China national daily BaP_{eq} standard (2.5 ng/m^3) but was higher than the international standard (1 ng/m^3) (Wang et al., 2012). The overall risks assessed were 2.36×10^{-6}, 1.93×10^{-6}, and 2.04×10^{-6} for $urban_1$, suburb, and $urban_2$, respectively, which was higher than the acceptable range (10^{-6}–10^{-4}), indicating that approximately 2–3 cases of cancer per million people can be due to the BaP exposure.

3.2. The profiles and levels of OH-PAHs and risk assessment

9 OH-PAHs were detected in > 50% of samples during whole exposure periods, except for 3-OH-Flu with a detection frequency (DF) of 27.8% in the suburb (Table 1). 6-OH-Chr and 3-OH-BaP were found in only a few samples (DF: 0–19%). The median concentrations of Σ_{12}OH-PAHs were 28.2, 16.8, and 21.4 μg/g Cr in $urban_1$, suburb, and $urban_2$, respectively. This was higher than that in adults from 26 cities in China (13.1 μg/L) (Huang et al., 2022) and New York State, USA (5.7 μg/g Cr) (Zhu et al., 2021), but subsequently lower than that of college students in Beijing (14.1 μg/mmol Cr) (Lin et al., 2016) and postgraduate students in Wuhan (10.0 μg/mmol Cr) (Li et al., 2019) (Tables S4 and S5). 1-OH-Pyr, as a classic biomarker, was detected at a frequency of 100% with median concentrations of 0.18, 0.19, and 0.18 μg/g Cr in $urban_1$, suburb, and $urban_2$, respectively. This level was lower than that of 26 cities in China (0.29 ng/mL) (Huang et al., 2022) and Guangzhou in 2018 (12.7 ng/mL) (Li et al., 2021). In conclusion, exposure to PAHs in Taiyuan is moderate.

No significant differences existed in the Σ_{12}OH-PAHs in urban and suburb ($p = 0.102$–0.316) (Table 1). However, the median concentration of 2-OH-Nap in the suburban area was 1.52 μg/g Cr, lower than the levels in the $urban_1$ and $urban_2$ area (3.41 and 3.14 μg/g Cr, $p < 0.05$). A similar trend was found for 3-OH-Flu. No significant differences were observed between other isomers in urban and suburbs. Coal-related emissions dominate the levels of PAHs in the atmosphere of Taiyuan, especially in winter. The relative humidity measured in the suburban area (69.3%) was higher than in the $urban_1$ and $urban_2$ areas (49.5% and 49.7%), which favors the deposition of PAHs and could lead to lower levels of OH-PAHs (Wang et al., 2010). Similar urban/suburban differences were reported in a previous publication (Cao et al., 2020a).

The effect of gender on the OH-PAHs concentrations during different periods was shown in Table S11. The results demonstrated that the concentrations of 2-OH-Nap and 1-OH-Nap were higher in females than in males at $urban_1$, suburban, and $urban_2$ locations, and this difference was particularly strong for 2-OH-Nap, with p values of 0.022, 0.001, and 0.03, respectively. What's more, when in the suburban location, females had higher levels of 1-OH-Nap ($p = 0.031$), 2-OH-Flu ($p = 0.002$), and Σ_{12}OH-PAHs ($p = 0.028$) than males. This is in contrast to the results of some previous cross-sectional studies (Huang et al., 2022; Li et al., 2021). Many factors influence the level of PAHs metabolism in the body, including dietary intake (Xia et al., 2010), ambient $PM_{2.5}$ concentrations (Li et al., 2019), personal time activity patterns (Maragkidou et al.,

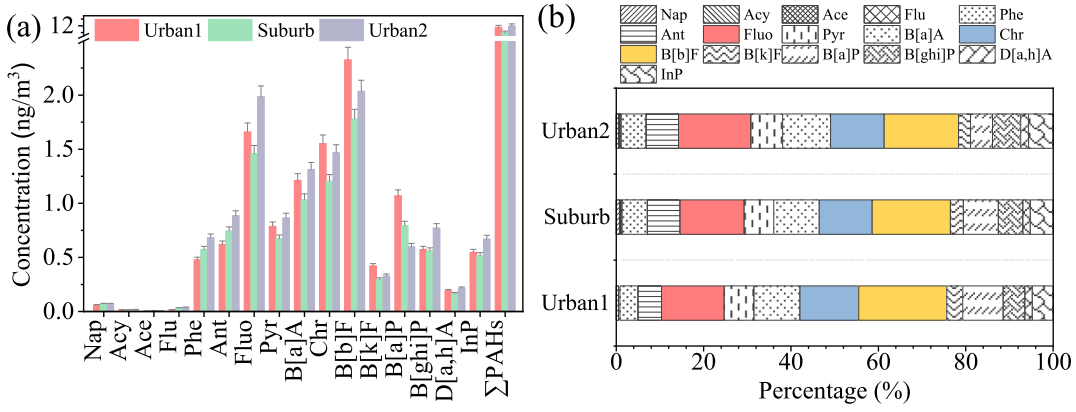

Fig. 1. Concentrations (a) and composition profiles (b) of PAHs during different periods.

Table 1
Urinary concentrations of OH-PAHs during different exposure periods (μg/g Cr).

	$Urban_1$			Suburb			$Urban_2$			*p* value		
	DF	Median	IQR	DF	Median	IQR	DF	Median	IQR	$Urban_1$ vs suburb	Suburb vs $urban_2$	$Urban_1$ vs $urban_2$
2-OH-Nap	100%	3.41	4.14	97.2%	1.52	2.72	100%	3.14	3.89	0.016	0.091	0.485
1-OH-Nap	100%	6.99	41.7	94.4%	2.58	10.2	97.2%	3.54	4.69	0.073	0.485	0.134
3-OH-Flu	55.6%	0.84	13.8	27.8%	nd	0.60	61.1%	0.96	14.0	0.015	0.004	0.615
2-OH-Flu	66.7%	0.19	0.39	61.1%	0.16	0.46	75.0%	0.24	0.63	0.809	0.188	0.362
2-OH-Phe	100%	1.55	1.01	100%	1.86	1.85	100%	1.25	0.89	0.131	0.005	0.070
3-OH-Phe	100%	0.93	0.55	100%	1.04	0.96	100%	0.73	0.58	0.112	0.002	0.066
4-OH-Phe	100%	1.48	0.97	100%	1.79	1.74	100%	1.21	0.90	0.137	0.005	0.081
1/9-OH-Phe	100%	1.47	0.96	100%	1.80	1.78	100%	1.22	0.88	0.149	0.006	0.079
1-OH-Pyr	100%	0.18	0.62	100%	0.19	0.09	100%	0.18	0.67	0.451	0.597	0.796
6-OH-Chr	nd	nd	0.00	5.56%	nd	0.00	16.7%	nd	0.00	0.154	0.160	0.011
3-OH-Bap	2.78%	nd	0.00	5.56%	nd	0.00	19.4%	nd	0.00	0.537	0.096	0.021
$\sum_{12}$OH-PAHs	100%	28.2	70.0	100%	16.8	20.0	100%	21.4	68.5	0.102	0.543	0.316

DF: detection frequency; nd: no detection.

2017), etc., which need to be further investigated.

The composition profiles of OH-PAHs in urban and suburban areas followed similar patterns. 1-OH-Nap (23.6% and 40.1%) was the most significant proportion of Σ_{12}OH-PAHs during $urban_1$ and $urban_2$ (Fig. S1b), followed by 2-OH-Nap (12.1% and 14.7%) and 2-OH-Phe (5.5% and 5.8%). 1-OH-Nap (15.4%) accounted for the highest percentage in the suburban location, followed by 2-OH-Phe (11.1%), 4-OH-Phe (10.7%), and 1/9-OH-Phe (10.7%), which was different from the distribution characteristics of external exposure. It might result from the differences in metabolic levels caused by PAHs entering the body through multiple pathways.

The total estimated daily intakes (TEDIs) of Σ_{12}OH-PAHs were 2.51, 1.64, and 2.12 μg/kg-bw/day in the $urban_1$, suburb, and $urban_2$, respectively (Table S6), which was comparable to that from subjects in southern China (Guangzhou) (1.30–12.7 μg/kg-bw/day) (Li et al., 2015). OH-Phe was the dominant component (0.22–0.42 μg/kg-bw/day), followed by OH-Nap (0.05–0.23 μg/kg-bw/day). OH-Flu and OH-Pyr accounted for a smaller percentage (0.06–0.1 μg/kg-bw/day). The trend was similar to that in other Asian countries (Guo et al., 2013). The carcinogenic risk calculated by OH-PAHs was presented in Table S7. The CR ranged from 7.48×10^{-8}–1.07×10^{-5}, suggesting that residents in Taiyuan pose a potential cancer risk under the current exposure level. The median carcinogenic risk of Pyr in the suburb (4.18×10^{-7}) was lower than in the urban (5.14×10^{-7} and 7.05×10^{-7}).

3.3. Correlations between OH-PAHs and health effects

For lung function, a significant reduction was found in FVC levels from suburb to $urban_2$ ($p < 0.05$) with median values of 2780 and 2640 mL/s (Fig. 2a). A similar finding was also obtained for suburb FEV_1 ($p < 0.05$). However, the differences in other lung function parameters between different exposure periods were insignificant (p = 0.084–0.972). As for other health effect indicators, the result showed a substantial decline for 8-OHdG and IL-8 from $urban_1$ to suburb. This significant decreasing trend continued from suburb to $urban_2$ ($p < 0.001$) (Fig. 2b). There was a significant difference in median levels of FeNO in $urban_1$, suburb and $urban_2$, with concentrations of 10, 15, and 11 ppb, respectively. Moreover, concentrations of MDA at three stages (9.21, 12.5, and 6.25 pg/mL, respectively) differed significantly ($p < 0.05$). FeNO, 8-OHdG, MDA, and IL-8 levels in the suburb were higher than in the $urban_2$ ($p < 0.001$). This may be because, despite low levels of OH-PAHs in suburban areas, different activity intensities and passive smoking exposure to high concentrations of NO may lead to reduce NO production in the lungs due to a negative feedback loop (Cao et al., 2020a; Zhou et al., 2018a). In addition, environmental tobacco smoke has many carcinogens and oxidants that can lead to oxidative damage of lipids, which became a confounder of urinary metabolism levels (Kuang et al., 2013).

No significant correlations were found between OH-PAHs and health effects in the $urban_1$ period (Tables S8 and S9). However, 2-OH-Nap correlated with FeNO ($r = -0{,}434$, $p < 0.01$) and IL-8 ($r = -0.422$, $p < 0.05$) in the suburban area. Previous studies have demonstrated that high levels of PAHs exposure may cause an inflammatory response (Li et al., 2019). There were positive correlations between 2-OH-Nap and 8-OHdG ($r = 0.338$, $p < 0.05$) and MDA ($r = 0.419$, $p < 0.05$) in the suburban location. 2-OH-Nap was significantly correlated with 8-OHdG ($r = 0.348$, $p < 0.05$) during the $urban_2$. It has been suggested that PAHs exposure would lead to DNA damage. 1-OH-Pyr is significantly correlated with FVC and FEV_1 when being in the suburban location and $urban_2$. Moreover, 1-OH-Pyr is significantly correlated with PEF ($r = -0.419$, $p < 0.05$), PEF_{25} ($r = -0.502$, $p < 0.01$), and PEF_{50} ($r = -0.350$, $p < 0.05$) during the suburb period. In addition, OH-Phe has a significant

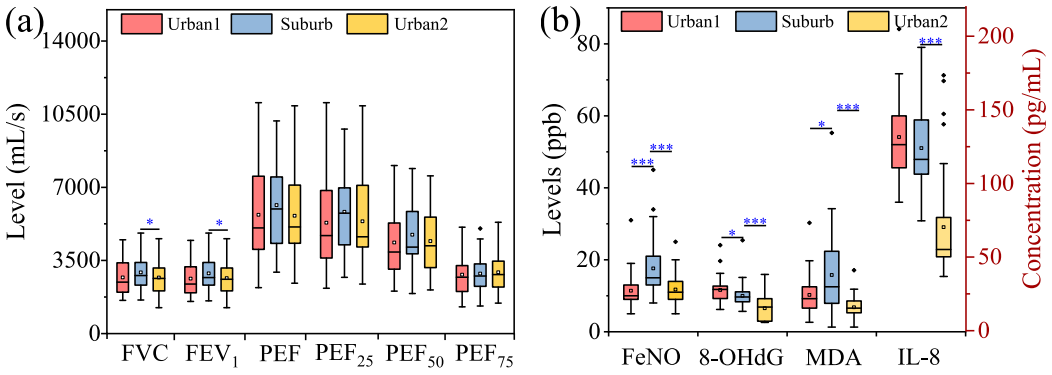

Fig. 2. The health effect indicators of subjects in different exposure periods. (a) Lung function and (b) FeNO and serum biomarkers. The star symbol means significant differences between groups (*: $p < 0.05$; ***: $p < 0.001$).

positive correlation with PEF_{50} and PEF_{75} during $urban_2$. This suggests that OH-PAHs can potentially affect health effects, including lung function, respiratory health, inflammatory factors, and oxidative stress, but the correlation varies due to different levels of OH-PAHs at different exposures.

3.4. Association between OH-PAHs and health effects

A linear mixed-effects model was used to determine relationships between the OH-PAHs levels and health effects at all three stages. There was a negative correlation between urinary 2-OH-Nap and FeNO ($\beta = -0.06$, $p < 0.05$). 2-OH-Flu was significantly negatively associated with FVC and FEV_1 ($p < 0.001$). Our results were consistent with many previous studies. A study from the Wuhan-Zhuhai cohort indicated that high and low molecular weight OH-PAHs were associated with FEV_1 (Zhou et al., 2018b). Linear mixed regression, including two communities in Wuhan, showed that multiple three-day mean levels of OH-PAHs, especially OH-Phe species, were significantly and negatively associated with FVC and FEV_1 (Hou et al., 2020). A cross-sectional survey of 629 coke oven workers in 2017 showed elevated total OH-PAHs was associated with lower percentage of predicted forced vital capacity among high fasting plasma glucose workers (Liu et al., 2022). What is more, all of the OH-Phe were significantly positively associated with FeNO, PEF_{25}, PEF_{50}, 8-OHdG, and IL-8 ($p < 0.05$) (Figs. S2, S3, and Table S10), respectively. It was demonstrated that OH-Phe plays an important role as an exposure marker in the respiratory damage caused by PAHs exposure. This result is in agreement with the literatures (Shi et al., 2021; Zhou et al., 2018a).

Further analysis of the differences in the regressions for different exposure periods was carried out (Figs. 3 and 4). With a unit 2-OH-Flu increase, FVC was reduced by 18.7% ($p = 0.139$), 5.6% ($p = 0.279$), and 10.9% ($p < 0.05$) at $urban_1$, suburb, and $urban_2$, respectively. A per unit increase of 2-OH-Flu was also significant with a 10.6% ($p < 0.05$) decrease of FEV_1 in $urban_2$. Moreover, the relationships between 1-OH-Pyr and FVC, FEV_1, and PEF_{25} all show a decreasing and then increasing trend. FVC and FEV_1 can be used to characterize pulmonary ventilation function and are key indicators for diagnosing airway disease (Zhou et al., 2018b). Airway epithelial cells directly defend against inhaled foreign bodies or particulate matter (Cao et al., 2020b). When PAHs enter the respiratory tract through inhalation, the increased lipophilicity of organic compounds decreases the rate of absorption through the tracheobronchial epithelium diffusing into the circulatory system (Bostrom et al., 2002). Due to the long retention time of lipophilic compounds in the epithelium at the entry site, the metabolic transformation is considerable even at low enzymatic activity. Therefore, an increase in

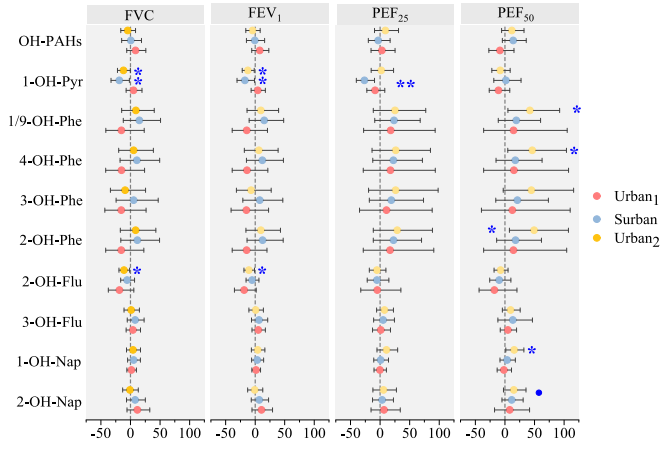

Fig. 3. Percentage change of lung function associated with urinary PAH metabolites during different periods (N = 36). Adjusted for sex, age, and body mass index. (•: $p < 0.1$; *: $p < 0.05$; **: $p < 0.01$).

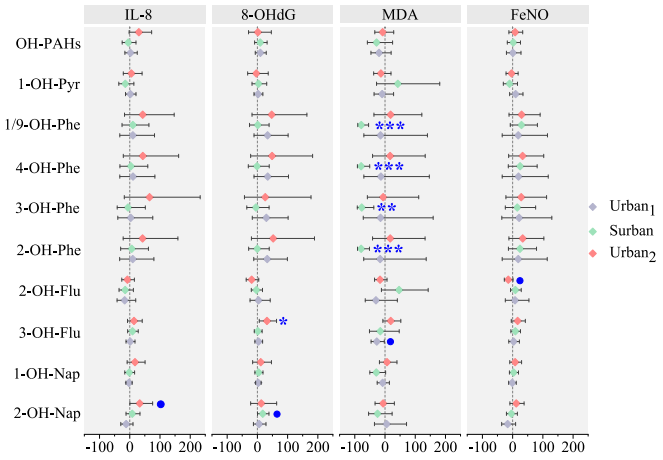

Fig. 4. Association of urinary PAH metabolites with FeNO, oxidative stress, and inflammatory factors during different periods ($N = 36$). Adjusted for sex, age, and body mass index. (•: $p < 0.1$; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$).

local concentrations in airway target cells can be expected. The toxicity of pollutants and their metabolites reduces lung function and increases the risk of airway inflammation. Though the coefficient was not always significant, it showed a trend of decreasing and increasing changes. In conclusion, exposure to PAHs can reduce human lung function, and low suburban exposure may attenuate this damage.

FeNO was changed by 14.2% ($p = 0.054$) with per unit 2-OH-Flu increase at the $urban_2$. With the increase per unit 3-OH-Phe, a change of 21.7%, 15.5%, and 28.6% FeNO were shown at the three exposure stages ($p > 0.05$), respectively. FeNO increased with 3-OH-Phe and 4-OH-Phe during the suburb and $urban_2$ periods, and the change in the suburb was lower than in $urban_2$. Short-term changes in pollutant exposure would trigger fluctuations in FeNO levels. This is consistent with the Wuhan-Zhuhai cohort study that PAHs stimulation may cause defense responses in the respiratory system (Zhou et al., 2018a). The most prominent source of exhaled NO is produced in the epithelium/endothelium by endothelial nitric oxide synthase. In pulmonary circulation, some signals indicate that NO is crucial in regulating vascular tone (Klinger et al., 2013). Moreover, extra NO can be released during the inflammatory process by inducible NOS from immune cells (Wang et al., 1998). Higher concentrations of PAHs in urban can deposit directly on the thin alveolar epithelium (Bostrom et al., 2002), leading to an enhanced airway inflammatory response and therefore elevated FeNO levels (Zhou et al., 2018a). In contrast, after traveling to a suburban area with lower levels of PAHs exposure, the estimated effects of elevated FeNO levels are less than during urban exposure, indicating that the level of this inflammatory response is reduced in suburban areas.

Per unit change of 2-OH-Phe, 3-OH-Phe, 4-OH-Phe, and 1/9-OH-Phe was significantly associated with 78.7% ($p < 0.001$), 76.9% ($p < 0.01$), 78.9% ($p < 0.001$), and 78.5% ($p < 0.001$) MDA decrease when being in the suburban location. The unexpected inverse associations could reflect an immunosuppressive effect, evidenced by some PAHs in animal studies (Reynaud and Deschaux, 2006). Like FeNO, most of the coefficients between OH-Phe and IL-8 were positive, and the values for suburban exposure were smaller than the results for urban exposure. For 8-OHdG, each unit increase of 2-OH-Nap was positively associated with an 18.5% ($p = 0.053$) and 13.1% ($p = 0.455$) increase in 8-OHdG levels during the suburban and $urban_2$ periods. PAHs produced a large amount of ROS in various metabolic steps. Elevated levels of ROS can accelerate DNA damage in epithelial cells, causing an upregulation of p53 and transforming growth factor β (TGF-β) as well as secretion of different factors from fibroblasts stimulating apoptotic pathways (Gao et al., 2015). Cell turnover balance may thus be disrupted with the generation of fibrosis (Plataki et al., 2005), leading to reduced pulmonary

compliance and other impaired functions. Moreover, higher than normal levels of oxidative stress occurred in the lung epithelium of some pneumonia patients, a condition that induces DNA damage and apoptosis (Kuwano et al., 2003). Thus, when traveling from $urban_1$ to suburb, decreased OH-PAHs in subjects lead to a decrease in the level of 8-OHdG, so there is a mitigating effect on the decline in 8-OHdG. This mitigating effect disappears when returning to the $urban_2$, increasing the magnitude of the decrease. The changing trend of post-elevation can fully indicate that exposure to high mountains will partially suppress the production of respiratory symptoms to protect human health.

The FVC and FEV_1 were changed by 21.1% and 18.2% ($p < 0.05$) with per unit 8-OHdG increase in Fig. S4. With per unit IL-8 increase, FVC and FEV_1 were raised by 38.7% and 34.3% ($p < 0.001$). Meanwhile, a significant association of IL-8 with FEV_1/FVC (3.03%, $p < 0.05$), PEF (34.3%, $p < 0.01$), and PEF_{25} (27.6%, $p < 0.05$) were found, respectively. However, there was no significant association between MDA and lung functions. The mediated proportion by 8-OHdG in the relationship between 2-OH-Phe, 3-OH-Phe, 4-OH-Phe, and 1/9-OH-Phe and FVC was 50.4%, 52.8%, 50.8%, and 49.9%, respectively (Table S12). In addition, 8-OHdG also has mediated effects on the association between these OH-Phe (1/2/3/4/9-OH-Phe) and FEV_1. A similar result was found for IL-8. For FeNO, there were significant mediated effects on the relationships between 3-OH-Phe, 4-OH-Phe, and 1/9-OH-Phe and FVC and FEV_1. OH-Phe, as the high-molecular-weight PAH metabolites, contains high toxic, carcinogenic and mutagenic activities (Kim et al., 2013), which may contribute to high oxidative DNA damage (Cao et al., 2020b).

There are some limitations in this article. First, our relatively small sample size may have limited the statistical power and led to an insignificant correlation between OH-PAHs levels and health indicators at the three stages. In addition, the external exposure concentrations in this study were obtained based on the detection of air samples collected from fixed locations, which, although widely used, were less accurate than those measured by personal monitors, which may inevitably lead to errors and render the study results invalid. In addition, other major pollutants, such as benzenes, may also affect respiratory health. Unfortunately, however, our study did not measure them; finally, our findings are based on college students in their 20s. Future experimental studies need to be conducted in more sensitive groups, such as children and the elderly, to validate and generalize our findings.

4. Conclusion

This study demonstrated that urinary 2-OH-Phe, 3-OH-Phe, 4-OH-Phe, and 1/9-OH-Phe of healthy students in Taiyuan were significantly positively associated with FeNO, 8-OHdG, and IL-8. Moreover, increased 2-OH-Flu was associated with decreased FVC, FEV_1, 8-OHdG, and IL-8. These surveys emphasize reducing PAH exposure to protect lung function and prevent airway or systemic inflammation and oxidative damage. The effect parameters showed a trend of first decreasing and then increasing, indicating that short-term exposure in the alpine region of Taiyuan can clean the pollution and protect the health of the respiratory system. This could have significant implications for exploring potential respiratory biomarkers in PAHs exposure.

CRediT authorship contribution statement

Huilin Zhang: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Ranran Liu:** Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Liu Yang:** Data curation, Writing – review & editing. **Hong Cheng:** Writing – review & editing. **Shengchun Wang:** Writing – review & editing. **Bin Zhang:** Writing – review & editing. **Jiyuan Shao:** Writing – review & editing. **Shengtao Ma:** Validation, Writing – review & editing. **Dan Norbäck:** Validation, Writing – review & editing. **Xin Zhang:** Validation, Funding acquisition, Supervision, Project administration. **Taicheng An:** Validation, 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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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