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Obesity mediated the association of exposure to polycyclic aromatic hydrocarbon with risk of cardiovascular events

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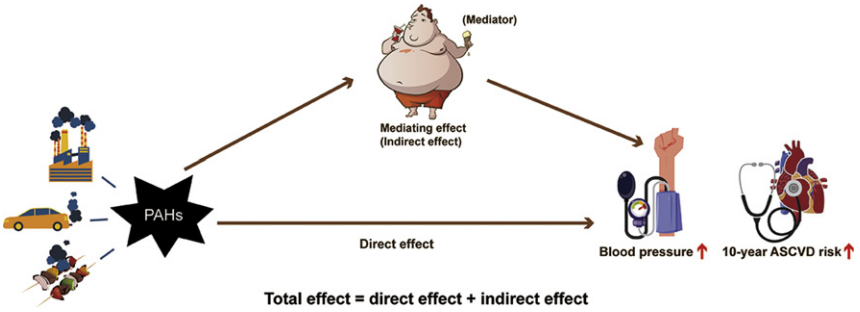
HIGHLIGHTS

- Urinary OH-PAHs levels were positively associated with blood pressure.
- Urinary OH-PAHs levels were associated with increased 10-year ASCVD risk.
- Obesity might mediate the association of PAHs exposure with the 10-year ASCVD risk.

GRAPHICAL ABSTRACT



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ABSTRACT

Exposure to polycyclic aromatic hydrocarbons (PAHs) could cause high blood pressure (BP) and increased risk for atherosclerotic cardiovascular disease (ASCVD). However, the mechanisms underlying the relationship between them were unclear. We investigated potential mediation effect of obesity on the association of exposure to PAHs with high BP and increased risk for ASCVD. In the repeated measures study, 106 community-dwelling residents in Wuhan, China finished the physical examination in the winter and summer seasons, eight urinary PAHs metabolites were measured. Associations of urinary PAHs with high BP and increased risk for ASCVD were assessed using either linear mixed effect models or generalized estimating equations models. Mediation analysis was performed to evaluate the mediating effect of obesity on the association of urinary PAHs metabolites with high BP or increased risk of ASCVD. We observed the positive association between urinary PAHs metabolites and BP or the odds ratios for high BP (all $P < 0.05$). Additionally, each one-unit increase in ln-transformed urinary

Abbreviation: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; BaP_{TEQ}, toxic equivalent concentration of benzo[*a*]pyrene; CI, confidence interval; CVD, cardiovascular diseases; DI, daily intakes; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HC, hip circumference; HDL-C, high density lipoprotein cholesterol; ICC, intra-class correlation coefficient; IQR, interquartile range; LDL-C, low density lipoprotein cholesterol; OH-PAHs, monohydroxylated PAHs metabolites; PAHs, polycyclic aromatic hydrocarbons; $PM_{2.5}$, fine particulate matter; OR, odds ratio; SBP, systolic blood pressure; TG, triglyceride; TC, total cholesterol; TyG, triglyceride glucose index; TyG-BMI, combined TyG and BMI; TyG-WC, combined TyG and WC; VAI, visceral adiposity index; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; 2-OHNa, 2-hydroxynaphthalene; 2 + 3-OHFlu, 2-hydroxyfluorene and 3-hydroxyfluorene; 2 + 3-OHPh, 2-hydroxyphenanthrene and 3-hydroxyphenanthrene; 4-OHPh, 4-hydroxyphenanthrene; 9-OHPh, 9-hydroxyphenanthrene; 1-OHP, 1-hydroxypyrene; ∑OH-PAHs, the total of PAH metabolites.

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levels of 4-hydroxyphenanthrene or the total of PAH metabolites was associated with a 12.63% or 11.91% increase in the estimated 10-year ASCVD risk (both $P < 0.05$). The waist-to-height ratio mediated 29.0% of the association of urinary 4-hydroxyphenanthrene with increased risk of ASCVD ($P < 0.05$). The findings suggest that PAHs exposure may be associated with elevated BP and an increased risk of ASCVD. Obesity may partially mediate the association between PAHs exposure and higher BP or increased risk of ASCVD.

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are typical kinds of persistent organic pollutants (POPs), sixteen kinds of them are considered as priority pollutants by the US Environmental Protection Agency and European Agencies. Human populations can be exposed to PAHs via inhalation, ingestion and dermal routes, because PAHs are produced from incomplete combustion of coal, petroleum products and exhaust of diesel vehicles as well as tobacco smoking, cooking fumes and grilled food (Boström et al., 2002; Srogi, 2007). PAHs are known as toxic, mutagenic, carcinogenic contaminants in the environment, however, the health consequences of long-term exposure to low-dose PAHs in non-occupationally exposed population were fully unknown. Previous studies suggested that exposure to ambient particulates were associated with the development of atherosclerosis and increased risk of cardiovascular diseases (CVD) (Araujo et al., 2008). Increasing evidence from epidemiological studies has shown a relationship between non-occupational exposure to PAHs and higher CVD risk (Alshaarawy et al., 2016; Xu et al., 2013).

Urinary monohydroxylated PAHs metabolites (OH-PAHs) are considered as biomarkers to quantify personal exposure to PAHs. Of which urinary 1-hydroxypyrene (1-OHP) is widely considered as an internal exposure index reflecting PAHs exposure in occupational population (Brucker et al., 2014), however, it is very limited to reflect exposure of all kinds of PAHs in the environment using it only, because most PAHs are of different chemical structures and toxicities (Kim et al., 2013). Therefore, several OH-PAHs in urine have been regarded as biomarkers for assessing human exposure to environmental PAHs (Li et al., 2010).

The underlying mechanisms regarding how PAHs affect the development of atherosclerosis and increased risk for CVD remain unclear. Possible mechanisms are PAHs-induced oxidative stress as well as inflammation and atherogenic responses, which may accelerate the process of atherosclerosis and increase the risk of cardiovascular events (Araujo et al., 2008; Clark et al., 2012). Previous studies implicated that inflammatory indicators, such as white blood cell count and C-reactive protein were important predictors of CVD (Alshaarawy et al., 2013; Clark et al., 2012). The others suggested that obesity in relation to insulin resistance (IR) and visceral inflammation/adiposity might affect the

Table 1
Characteristics of the study population.

Category	Winter of 2014 (clinical visit 1, $n = 106$)	Summer of 2015 (clinical visit 2, $n = 103$)[c]
Gender (male/female, *n*, %)	48/58 (45.3/54.7)	46/57 (44.7/55.3)
Age (<18/18-/≥60 years, *n*, %)	24/43/39 (22.6/40.6/36.8)	24/41/38 (23.3/39.8/36.9)
Education (<7/7-/10-/≥13 years, *n*, %)	21/23/44/18 (19.8/21.7/41.5/17.0)	20/23/44/16 (19.4/22.3/42.7/15.6)
Smoking status[d]		
Active smoking (never/former/current, *n*, %)	89/6/11 (84.0/5.6/10.4)	87/5/11 (84.5/4.8/10.7)
Passive smoking (yes/no, *n*, %)	42/64 (39.6/60.4)	41/62 (39.8/60.2)
Alcohol use (yes/no, *n*, %)[d]	16/90 (15.1/84.9)	16/87 (15.5/84.5)
Physical activity (yes/no, *n*, %)	64/42 (60.4/39.6)	66/37 (64.1/35.9)
Self-cooking (yes/no, *n*, %)	43/63 (40.6/59.4)	42/61 (40.8/59.2)
BMI (kg/m^2, mean ± SD)	23.71 ± 4.21	23.25 ± 4.20
WC (cm, mean ± SD)*	84.33 ± 12.55	80.73 ± 12.88
HC (cm, mean ± SD)*	98.48 ± 9.81	94.06 ± 9.32
WHR (mean ± SD)	0.86 ± 0.09	0.85 ± 0.08
WHtR (mean ± SD)*	0.52 ± 0.08	0.50 ± 0.07
Heart rate (time/min, mean ± SD)*	82.08 ± 12.76	78.55 ± 12.42
Blood pressure		
SBP (mm Hg, mean ± SD)*	129.25 ± 20.23	123.91 ± 24.14
DBP (mm Hg, mean ± SD)*	76.22 ± 11.00	72.81 ± 13.24
TG (mmol/L, median, IQR)	1.01 (0.75, 1.44)	1.06 (0.82, 1.78)
TC (mmol/L, median, IQR)	4.67 (3.90, 5.61)	4.37 (3.62, 5.16)
HDL-C (mmol/L, mean ± SD)*	1.27 ± 0.29	1.17 ± 0.22
LDL-C (mmol/L, mean ± SD)*	2.93 ± 1.03	2.59 ± 0.99
FPG (mmol/L, median, IQR)*	5.45 (5.14, 5.81)	5.10 (4.73, 5.46)
VAI (median, IQR)	1.32 (0.84, 2.24)	1.43 (1.02, 2.43)
TyG (mean ± SD)	8.50 ± 0.61	8.52 ± 0.58
TyG-BMI (mean ± SD)	202.97 ± 45.48	200.47 ± 45.66
TyG-WC (mean ± SD)	723.19 ± 147.56	693.04 ± 143.06
ASCVD risk 1[a] (%, median, IQR)	6.80 (2.22, 13.97)	6.01 (2.35, 14.00)
ASCVD risk 2[b] (%, median, IQR)	9.34 (3.96, 15.86)	7.79 (3.83, 13.56)

ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; IQR: interquartile range; WC: waist circumference; HC: hip circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglyceride; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C low density lipoprotein cholesterol; FPG fasting plasma glucose; VAI: visceral adiposity index; TyG: triglyceride glucose index; TyG-BMI: combined TyG and BMI; TyG-WC: combined TyG and WC.

[a] The estimated 10-year risk for development of ASCVD among participants aged 40 to 79 years using comprehensive multivariable risk equations for nonHispanic **White-American** in the panel study (***n* = 59**). Among the 106 participants, 59 ones aged 40 to 79 years finished the physical examinations repeatedly in the two seasons.

[b] The estimated 10-year risk for development of ASCVD among participants aged 40 to 79 years using comprehensive multivariable risk equations for nonHispanic **African-American** in the panel study (***n* = 59**). Among the 106 participants, 59 ones aged 40 to 79 years finished the physical examinations repeatedly in the two seasons.

[c] Two subjects gave up the physical examinations owing to changing their workplaces, another one died of choking of foreign bodies stuck throat.

[d] Smoking status and alcohol use were defined as described elsewhere (Yang et al., 2014).

* $P < 0.05$. Student's *t*-test was used to compare normal distribution of continuous variables between two clinical visits.