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Association of polycyclic aromatic hydrocarbons exposure with atherosclerotic cardiovascular disease risk: A role of mean platelet volume or club cell secretory protein☆

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ABSTRACT

Background: Inflammation may play an important role in the association between exposure to polycyclic aromatic hydrocarbons (PAHs) and atherosclerotic cardiovascular disease (ASCVD) risk. However, the underlying mechanisms remain unclear.

Objectives: To investigate the association of PAHs exposure with ASCVD risk and effects of mean platelet volume (MPV) or Club cell secretory protein (CC16) on the association.

Methods: A total of 2022 subjects (689 men and 1333 women) were drawn from the baseline Wuhan residents of the Wuhan-Zhuhai Cohort study. Data on demography and the physical examination were obtained from each participant. Urinary monohydroxy PAH metabolites (OH-PAHs) levels were measured by a gas chromatography-mass spectrometry. We estimated the association between each OH-PAHs and the 10-year ASCVD risk or coronary heart disease (CHD) risk using logistic regression models, and further analyze the mediating effect of MPV or plasma CC16 on the association by using structural equation modeling.

Results: The results of multiple logistic regression models showed that some OH-PAHs were positively associated with ASCVD risk but not CHD risk, including 2-hydroxyfluoren ($\beta = 1.761$; 95% CI: 1.194−2.597), 9-hydroxyfluoren ($\beta = 1.470$; 95% CI: 1.139−1.898), 1-hydroxyphenanthrene ($\beta = 1.480$; 95% CI: 1.008−2.175) and ΣOH-PAHs levels ($\beta = 1.699$; 95% CI: 1.151−2.507). The analysis of structural equation modeling shows that increased MPV and increased plasma CC16 levels contributed 13.6% and 15.1%, respectively, to the association between PAHs exposure and the 10-year ASCVD risk ($p < 0.05$).

Conclusions: Exposure to PAHs may increase the risk of atherosclerosis, which was partially mediated by MPV or CC16.

Abbreviations: ASCVD, arteriosclerotic cardiovascular disease; BMI, body mass index; CC16, Club cell secretory protein; CFI, comparative fit index; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; IQR, interquartile range; MPV, mean platelet volume; OR, odd ratios; PAHs, polycyclic aromatic hydrocarbons; PDW, platelet distribution width; RMSEA, root mean square error approximation; SEM, structural equation modeling; SD, standard deviation; WBC, white blood cell.

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1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) is a collective term comprising of a group of disorders of the heart and blood vessels. It is well recognized as a chronic inflammatory disease (Taleb, 2016). In the development of atherosclerosis, occurrence of endothelial dysfunction is related to the two major initiators to inflammation, including vascular effect of reactive oxygen species and lipid oxidation (Ellulu et al., 2016). Adverse health effects of exposure to air pollution have attracted great scientific interest due to increased risk of atherosclerosis in relation to air pollution, besides dietary and lifestyle, obesity, type 2 diabetes and genetic factors. Several researches have revealed that exposure to airborne polycyclic aromatic hydrocarbons (PAHs) may play an important role in the pathological lesions of atherosclerosis, hypertension, cardiometabolic impairment and arterial inflammation (Alshaarawy et al., 2016; Freitas et al., 2014; Poursafa et al., 2017; Xu et al., 2013).

Inflammation is a process of the body's natural response to injury, including vascular hyperpermeability, white cell accumulation and vascular remodeling. The *in vivo* and *in vitro* studies indicated that exposure to PAHs was positively associated with inflammatory response (Albert et al., 1977; Alshaarawy et al., 2013; Clark et al., 2012). Moreover, endogenous and exogenous factors (such as angiotensin-II and environmental pollution) can trigger oxidative stress and releases of inflammatory cytokines (such as interleukin 1β and tumor necrosis factor alpha), leading to endothelial dysfunction, decrease in relaxation of smooth muscle cell and intima-media thickening of the carotid artery. While endothelial dysfunction may be involved in the initiation of vascular inflammation and development of vascular remodeling, it may accelerate both plaque progression and instability in the pathogenesis of atherosclerosis (Ellulu et al., 2016). Thus, inflammation is considered as an early event in the progression of atherosclerosis.

Mean platelet volume (MPV) as a diagnostic marker reflects the platelet size and the rate of platelet production. It may be a mediator in the process of inflammation regarding cardiovascular disease, periodontal inflammation, familial Mediterranean fever and arthritis (Basaran et al., 2017; Boilard et al., 2010; Sansanayudh et al., 2014; Zhan et al., 2017). Larger platelets are more reactive and younger, which contain more α-granules and thus produce more thromboxane A_2. The migrated platelets in the inflammatory sites are then intensely consumed (Thompson and Jakubowski, 1988). Club cell secretory protein (CC16), a 16 kDa homodimeric protein, is secreted by the non-ciliated bronchiolar club cells. Serum CC16 was considered as a valid marker of the distal airway damages by air pollution (Lakind et al., 2007), because it reflected damaging processes at the air-blood barrier and altered lung epithelial permeability (Broeckaert and Bernard, 2000), and had anti-inflammatory properties. Increased serum CC16 levels were found in individuals exposed to fine particulate matter, smoke from combustion of polypropylene and ambient ozone (Bernard et al., 1997; Broeckaert et al., 2000; Wang et al., 2017). Thus, serum CC16 levels may have a great potential for assessing the extent of inflammation or tissue damage and health risk among individuals with cardiopulmonary dysfunction.

Several cardiovascular risk prediction models have been used in clinical practice to identify and treat high-risk populations, including the Framingham Risk Score (FRS) (D'Agostino et al., 2008), the American College of Cardiology and the American Heart Association (ACC/AHA) (Goff et al., 2014) and the World Health Organization/International Society of Hypertension (WHO/ISH) (Mendis et al., 2007) models. However, these models may overestimate 10-year CVD risk in Chinese population, because they were derived from data obtained from Western participants (Table S1). In the present study, we used the Chinese Multiprovincial Cohort Study (CMCS) and the Prediction for Atherosclerotic Cardiovascular Disease Risk in China Project (the China-PAR Project) models to predict the 10-year coronary heart disease (CHD) risk and ASCVD risk, and structural equation modeling was further constructed to analyze the affecting factors of the ASCVD risk and CHD risk, including urinary monohydroxylated PAHs metabolites (OH-PAHs), MPV and plasma CC16. Our research may provide a clue to explain the association between PAHs exposure and the 10-year ASCVD risk.

2. Materials and methods

2.1. Study population

A total of 2715 individuals aged 30–74 years who were recruited from the baseline Wuhan residents (n = 3053) of the Wuhan-Zhuhai (WHZH) Cohort Study (Song et al., 2014), because the 10-year risks of ASCVD and CHD were estimated based on the age group. After excluding those with missing data on urinary OH-PAH concentrations (n = 207), body mass index (BMI, n = 30), white blood cell (WBC, n = 24), mean platelet volume (MPV, n = 108), Club cell secretory protein (CC16, n = 308), self-reported angina (n = 29), myocardial infarction (n = 18) and stroke (n = 37), 2022 participants (689 men and 1333 women) were finally included in this study. Table S2 showed that there were significant differences in the distributions of age (p = 0.002), gender (p = 0.035), educational levels (p = 0.000), active smoking (p = 0.037), transportation time on the way (p = 0.004), self-cooking meals (p = 0.000) and CC16 (p = 0.004) between participants and non-participants. However, gender, educational levels, active smoking, transportation time on the way and self-cooking meals were considered as potential confounders.

All participants took part in questionnaires and basic physical examination, and provided their blood and urine samples on the physical examination day. Information on demographic characteristics, occupational history, personal and family medical history and lifestyle habits including active and passive smoking, alcohol consumption, physical activity and self-cooking meals were collected using standardized questionnaires by trained reviewers. Non-smokers were defined as those who had smoked less than one cigarette per day in the past 6 months, otherwise, they were considered as smokers. Passive smokers were defined as those who exposed to tobacco smoke indoor environment at least once a week for at least 15 min each time. Nondrinkers were defined as those who had drunk alcohol less than once each week in the past six months; otherwise, they were considered as drinkers. Physical activity was defined as regularly doing at least 20 min of physical activity during leisure time over the previous 6 months (yes or no). Furthermore, those were same described in our previous work (Hou et al., 2017). Height and body weight were measured with light indoor clothing and without shoes. Waist circumference (WC) was measured at a vertical level 1 cm above the navel. Body mass index (BMI) was calculated as kilograms per squared meters (kg/m^2). Participants were classified into three groups: non-obese (<24 kg/m^2), overweight (24–28 kg/m^2) and obese (≥28 kg/m^2) using body mass index cut-off points, which was recommended by the Working Group on Obesity in China. Hypertension was defined as diastolic blood pressure (DBP) ≥ 90 mmHg or systolic blood pressure (SBP) ≥ 140 mmHg, or self-reported hypertension diagnosed by a physician, or taking antihypertensive drugs. Diabetes was defined as fasting blood glucose value ≥ 7.0 mM or antidiabetic therapy.

This study was approved by Medical Research Ethics Committee of Tongji Medical College, Huazhong University of Science and