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Cardiometabolic traits mediated the relationship from urinary polycyclic aromatic hydrocarbons metabolites to heart rate variability reduction: A community-based study☆

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ABSTRACT

Polycyclic Aromatic Hydrocarbons (PAHs) exposure was related with metabolic syndrome (MetS) and heart rate variability (HRV) reduction, and HRV was also affected by cardiometabolic traits. However, the role of cardiometabolic traits in the associations from PAHs exposures to HRV was largely unknown. We conducted this study to investigate whether the relationship between PAHs exposure and HRV reduction was mediated by cardiometabolic traits. Levels of urinary polycyclic aromatic hydrocarbons metabolites (OH-PAHs), 10min-HRV, and metabolic traits were accurately measured for 2476 participants from Wuhan-Zhuhai (WHZH) cohort. Single mediator and multiple mediator models were used to evaluate the mediation effects of cadiometabolic traits. The concentrations of ΣOH-PAHs ranged from 4.20 to 8.63 mg/mmol Cr. When compared with the lowest tertile, ΣOH-PAHs in the highest tertile were significantly related with 20% (95% confidence interval [95%CI]:1%, 40%), 35% (95%CI: 14%, 56%), 22% (95% CI: 1%, 44%), and 38% (95%CI: 9%, 68%) decreases in very low frequency (VLF), low frequency (LF), high frequency (HF), and total power (TP) for participants with MetS, respectively. No statistically significant associations between ΣOH-PAHs and HRV indices were observed for participants without MetS. Similar results were found when we investigated the relationships between OH-PAHs and HRV indices by three groups of OH-PAHs (including total hydroxynaphthalene [ΣOHNa], total hydroxy fluorene [ΣOHFlu], and total hydroxyphenanthrene [ΣOHPh] metabolites). Further, mediation analysis suggested that cardiometabolic traits, including fasting glucose (GLU), high density lipoprotein (HDL), and blood pressure partially mediated the relationship from ΣOH-PAHs to HRV reduction. GLU was the strongest mediator, with mediation percentages of 15.70% for VLF, 14.70% for LF, 43.03% for HF, and 5.61% for TP. Our study found that the relationships between OH-PAHs and HRV reduction differed among participants with and without MetS, and these relationships were found to be partially mediated by cardiometabolic traits, especially fasting glucose. Further studies are encouraged to validate our findings and investigate potential mechanisms.

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are a group of toxic atmospheric pollutants, generated during incomplete combustion of carbon-containing materials such as fossil fuels, coal, cigarette smoking, and the cooking of food (Kim et al., 2013). PAHs have strong lipophilic properties making them quickly absorbed by the fatty tissues such as the kidney and liver within body and capable of being stored in fat cells and tissues containing fat (Abdel-Shafy

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and Mansour, 2016), and easily accumulated through repeated and long-term exposures or bio-accumulate through the food chain (Scinicariello and Buser, 2014; Simkhovich et al., 2008). Accumulating evidence showed that PAHs and their metabolites could impair endocrine systems or immunological systems and cause metabolic disturbances, inflammation and oxidative stress due to their carcinogenic and endocrine disrupting properties (Chen et al., 2008; Kuang et al., 2013; Li et al., 2015). Previous studies also identified significant associations between PAH exposure and metabolic syndrome (MetS), heart rate variability (HRV) reduction, and increased risks of cardiovascular diseases (CVD) (Brook et al., 2010; Byun et al., 2016; Feng et al., 2014; Hu et al., 2015; Pope et al., 2011; Yang et al., 2014). According to previous studies, MetS and HRV reduction are independent risk factors for CVD (Rovere et al., 1998; Thayer et al., 2010). HRV is a potential early indicator of adverse cardiovascular events (Chang et al., 2016; Ma et al., 2017). Additionally, cardiometabolic traits (especially fasting glucose [GLU]) are outstanding impact factors for HRV reduction an (Chang et al., 2016). It is thus possible that PAH exposure induce adverse cardiovascular events via metabolic disorders. However, no study has conducted to investigate the potential roles of cardiometabolic traits in the associations between PAH exposures and HRV reduction. Therefore, in the current study, we cross-sectionally investigated the roles of MetS and metabolic traits in the relationship between PAH exposure and HRV reduction in a community based population. Our objectives were to investigate whether the relationship between PAH exposure and HRV reduction was modified by MetS and to evaluate the mediation effects of cardiometabolic traits from PAH exposures to HRV reduction.

2. Materials and methods

2.1. Study population

The Wuhan-Zhuhai (WHZH) cohort with a sample size of 3053 participants in Wuhan city was launched in 2011. Participants were recruited from two representative communities (one in downtown and one in urban fringe area) using a stratified, cluster sampling approach which was well described previously (Song et al., 2014). In each community, people aged 18–80 years and living here for more than five years were invited to this study. Each Individual was asked to complete a questionnaire (including demographic, occupation, lifestyle, and medication information) via a face-to-face interview by trained interviewers and undergo a physical examination (including body measurements, respiratory function, HRV, blood routine, and urine routine) by specialists in 2011. Fasting peripheral blood samples and early morning urine samples were collected and stored at −80 °C and were later used to measure blood biomarkers and PAH metabolites. In the present study, a total of 577 participants were excluded due to missing data on OH-PAHs (248 participants under limits of detection), HRV (178 participants), MetS (60 participants) and covariates (91 participants). Finally, 2476 participants with complete data on OH-PAHs, HRV, MetS and covariates information in 2011 were included in the following analysis. Face-to-face interview and physical examination were performed in May 2011, and were lasted for 15 days. For each participant, urine sample and blood sample collection, blood routine measurement, and HRV measurement were performed in the same morning. HRV measurement was conducted in a sitting position with at least 10 min of rest after blood and urine sampling. The study protocol was approved by Huazhong University of Science and Technology (Wuhan, Hubei, China). All participants provided written informed consent.

2.2. Measurement of urinary PAH metabolites

PAHs exposure can be detecting using urinary polycyclic aromatic hydrocarbons metabolites (OH-PAHs). A total of 12 urinary OH-PAHs and creatinine were measured in a 3 ml fasting urine sample using gas chromatography-mass spectrometry method (Agilent 5975B/6890N GC-MS System, Agilent, Santa Clara, California) for each participant (Romanoff et al., 2006; Zhou et al., 2016). Among them, 10 non-carcinogenic metabolites (1-hydroxypyrene, 1-hydroxynaphthalene, 2-hydroxynaphthalene, 2-hydroxyfluorene, 9-hydroxyfluorene, 1-hydroxyphenanthrene, 2-hydroxyphenanthrene, 3-hydroxyphenanthrene, 4-hydroxyphenanthrene, and 9-hydroxyphenanthrene) were included in the final analysis, while the other two carcinogenic metabolites (6-hydroxychrysene and 3-hydroxybenzo[a]pyrene) were excluded because concentrations were always below the limits of detection (LOD). The LOD for the urinary OH-PAHs ranged from 0.1 to 0.9 mg/L. We summarized PAH metabolite as total hydroxynaphthalene (ΣOHNa = 1-hydroxynaphthalene+2-hydroxynaphthalene), total hydroxy fluorene (ΣOHFlu = 2-hydroxyfluorene+9-hydroxyfluorene), total hydroxyphenanthrene (ΣOHPh = 1-hydroxyphenanthrene+2-hydroxyphenanthrene+3-hydroxyphenanthrene+4-hydroxyphenanthrene+9-hydroxyphenanthrene), and total PAH metabolites (ΣOH-PAHs). Valid urinary PAH metabolites concentrations were adjusted for urinary dilution by correcting for creatinine and calculated as μg/mmol creatinine (Cr).

2.3. Measurement of HRV

HRV indices were measured by 3-channel digital Holter monitors (Lifecard CF; Del Mar Reynolds Medical, Inc., Whitney, Irvine, USA) with a 1024 samples/second sampling rate for 10 min (Feng et al., 2014; Yang et al., 2014). Participants with heart rates ranging from 40 to 100 beats per minute were included. ECG data were recorded automatically into a removable flash card and then processed using the Impresario and Cardio Navigator Plus software (Del Mar Reynolds Medical Inc., Whitney, Irvine, USA). Statistical analysis were based on a single consecutive 5-min segment during the middle portion of each 10-min electrocardiography record (180–480 s) (Malik et al., 1996). In this study, we used five frequency measures of HRV: low-frequency power (LF, 0.04–0.15 Hz), high-frequency power(HF, 0.15–0.40 Hz), very-low-frequency power (VLF, 0.0033–0.04 Hz), total power (TP,0.01–0.40 Hz) and LF/HF. VLF mainly reflects both vagal control of heart rate and the effect of the renin-angiotensin system, higher values of VLF are believed to reflect better autonomic function; LF is a measure of baroreflex function; and higher HF and TP reflect higher parasympathetic (vagal) influence (Goldstein et al., 2011).

2.4. Ascertainment of MetS

MetS was defined according to the diagnostic criteria proposed by the Adult Treatment Program III of the National Cholesterol Education Program (NCEP ATP III, 2005). Participants were defined as MetS patients if they met three or more of the following variables and cutoff points: (1) Fasting triglyceride ≥ 1.69 mmol/L (150 mg/dL); (2) HDL cholesterol: Men < 1.04 mmol/L (40 mg/dL), Women < 1.29 mmol/L (50 mg/dL); (3) Fasting glucose: ≥ 5.5 mmol/L (100 mg/dL); (4) Waist circumference: men ≥ 102 cm, women ≥ 88 cm; (5) Systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg. As there are different MetS diagnostic criteria available and the results might be affected by the way MetS was defined (Kaur, 2014), we therefore performed sensitivity analyses by defining MetS using the International