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Studying the effects of polycyclic aromatic hydrocarbons on peripheral arterial disease in the United States

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HIGHLIGHTS

- This study used urinary biomarkers, i.e. metabolites of PAHs, as objective measurements of exposure.
- The effects of PAHs on peripheral arterial disease (PAD) were examined among a large population-based sample.
- Our study for the first time suggests that exposure to PAHs may increase the risk of PAD independent of smoking.

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ABSTRACT

Purpose: Polycyclic aromatic hydrocarbons are a group of prevalent pollutants which are produced by incomplete combustion of organic materials such as coal, fuel, tobacco smoking and food cooking. The associations between exposures to polycyclic aromatic hydrocarbons (PAHs) and peripheral arterial disease (PAD) have not been well studied.
Methods: We used the 2001-2004 National Health and Nutrition Examination Survey (NHANES) to investigate the associations between eight monohydroxy urinary metabolites of four PAHs and PAD.
Results: In a logistic regression model, subjects within the middle and highest tertiles of fluorene metabolites, 2-hydroxyfluorene (2-FLUO) and 3-hydroxyfluorene (3-FLUO), and phenanthrene metabolites, 1-hydroxyphenanthrene (1-PHEN) and 2-hydroxyphenanthrene (2-PHEN), had significantly higher prevalence of PAD as compared to subjects within the lowest tertile after adjusting for cigarette smoking, diabetes mellitus and other covariates (For 2-FLUO, the 3rd tertile: OR = 2.22, 95% CI = 1.13–4.37, p for trend = 0.02; For 3-FLUO, the 3rd tertile: OR = 2.36, 95% CI: 1.16–4.77, p for trend = 0.02; For 1-PHEN, the 3rd tertile: OR = 1.84, 95% CI: 1.01–3.37, p for trend = 0.04; For 2-PHEN, the 3rd tertile: OR = 1.76, 95% CI: 1.07–2.88, p for trend = 0.03).
Conclusions: Our findings suggest that exposure to PAHs may increase the risk of PAD. Further studies are necessary to explore the associations between PAHs and PAD.

1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are organic toxic chemical compounds with fused aromatic rings, formed during incomplete combustion of organic materials such as coal and petroleum product combustion, cigarette smoking, food cooking and industrial activities such as asphalt paving and aluminum smelting (McClean et al., 2004; McGrath et al., 2007). PAHs are resistant to degradation and can bioaccumulate through the food chain (Mumtaz et al., 1996). Dietary intakes of PAHs, exposure to airborne PAHs such as polluted air or cigarette smoke, as well as dermal absorption are the main exposure routes of PAHs (Bentsen et al., 1998; Vanrooij et al., 1992). An exposure–response relationship between exposure to ambient air pollution, cigarette smoking and cardiovascular disease (CVD) has been suggested by recent epidemiological studies (Pope et al., 2011; Zhang et al., 2011). Since PAHs are a group of ubiquitous pollutants in air, they may play important roles in the relationship between cigarette smoking, ambient air pollution and CVD. Recent studies suggested that exposure to high levels of PAHs may increase rates of CVD in humans (Burstyn et al., 2005; Xu et al., 2010).

Abbreviations: PAHs, Polycyclic aromatic hydrocarbons; OH-PAHs, Monohydroxy urinary metabolites of PAHs; PAD, Peripheral arterial disease; CVD, Cardiovascular disease; ABI, Ankle–brachial index; NHANES, The National Health and Nutrition Examination Survey; 1-NAP, 1-hydroxynaphthalene; 2-NAP, 2-hydroxynaphthalene; 2-FLUO, 2-hydroxyfluorene; 3-FLUO, 3-hydroxyfluorene; 1-PHEN, 1-hydroxyphenanthrene; 2-PHEN, 2-hydroxyphenanthrene; 3-PHEN, 3-hydroxyphenanthrene; 1-PYR, 1-hydroxypyrene; ORs, Odds ratios; AORs, Adjusted odds ratios; CIs, Confidence intervals.

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Peripheral arterial disease (PAD) is a disease caused by plaque build-up in peripheral artery, usually in legs, which affects normal blood flowing. Its classic symptom is intermittent claudication. However, most patients do not have typical leg symptoms (Hirsch et al., 2001; McDermott et al., 2001). PAD approximately affects 8–10 million Americans and is a strong marker of atherosclerotic burden and cardiovascular risk and has been recognized as a coronary risk equivalent (Kim et al., 2012). The risk factors of PAD including older age, tobacco smoking, and diabetes mellitus have been well recognized (McDermott et al., 2001). The enduring environmental exposure to PAHs in the general population might be a potential risk factor of PAD. However, few studies have examined the associations between PAHs exposure and PAD.

In this study, we analyzed the data from the 2001–2004 National Health and Nutrition Examination Surveys to examine this relationship between exposure to PAHs measured by urinary metabolites of PAHs (OH-PAHs), and PAD measured by ankle–brachial index (ABI) after adjusting for potential confounders (cigarette smoking, diabetes mellitus, age and other important covariates in a large-scale population-based sample).

2. Methods

2.1. Study population

NHANES uses a complex, multistage sampling design to obtain nationally representative samples of the non-institutionalized U.S. civilian population (CDC, 2013). The NHANES surveys collect data from personal interviews, examinations, and laboratory tests of biological samples. The data have been released for public use in two-year increments since 1999. For NHANES 2001–2002, 13,156 persons were selected for the sample, 11,039 persons were interviewed (83.9%), and 10,477 (79.6%) underwent a physical examination in a Mobile Examination Center (MEC). For NHANES 2003–2004, 12,761 persons were selected for the sample, of whom 10,122 persons completed the interview (79.3%) and 9643 (75.6%) were examined in the MEC. The data from these two data-cycles were used and analyzed in this study. OH-PAHs were measured in a one third subsample of persons 6 years and older in each data cycle. ABI was measured in a subsample of persons 40 years and older in each data cycle. Each subsample was representative of the total population in each NHANES data cycle and the appropriate weight was calculated for the subsample after considering the additional stage of sampling, the unequal probability of selection and the non-response rate (CDC, 2013). For the present analysis, we selected all participants aged 40 years or older who were both tested for OH-PAHs and ABI during these two data cycles as the study population. We further excluded participants with an ABI ≥ 1.5 ($n = 5$), which is usually related to noncompressible blood vessels in the legs (Newman et al., 1993). A total of 1732 participants who aged 40 years and older and had both tests of OH-PAHs and ABI were finally analyzed in this study.

2.2. Dependent variable

Participants 40 years of age and older in the NHANES are asked to participate in the ABI exam. The ABI exam was performed by trained health technicians in a specially equipped room in the mobile examination center. The examination procedure and quality control are described in detail in the Lower Extremity Disease Procedures Manual (CDC, 2002). Participants lie supine on the exam table during the exam. Systolic pressure is measured on the right arm (brachial artery) and both ankles (posterior tibial arteries). Systolic blood pressure is measured twice at each site for participants aged 40–59 years and once at each site for participants aged 60 years and older by using a Parks Mini-Lab IV Doppler device, model 3100 (Parks Medical Electronics, Inc., Aloha, Oregon).

The ABI was automatically calculated by the computer system and verified by NCHS before data release. The right ABI was obtained by dividing the mean systolic blood pressure in the right ankle by the mean blood pressure in the arm. The left ABI was obtained by dividing the mean systolic blood pressure in the left ankle by the mean blood pressure in the arm. The lower number of left ABI and right ABI is used as the patient's overall ankle–brachial index (Kim et al., 2012).

The participant was considered as a prevalent PAD case if her/his overall ankle–brachial index was less than 0.90 (Selvin and Erlinger, 2004).

2.3. OH-PAHs measurements

OH-PAHs were obtained from the 2001–2004 NHANES data. The methods of measuring these chemicals have been described in detail previously (Li et al., 2006). Briefly, urine was collected from individuals ages 6 years and above in MEC. The urine specimens were then processed, and stored under appropriate frozen (−20 °C) conditions until they are shipped to National Center for Environmental Health for testing. The procedure involved enzymatic hydrolysis of urine, solid-phase extraction, derivatization, and analysis using capillary gas chromatography combined with high-resolution mass spectrometry (GC/HRMS). This method used isotope dilution with ^{13}C-labeled internal standards. Ions from each analyte and each ^{13}C-labeled internal standard were monitored, and the abundances of each ion were measured. The ratios of these ions were used as criteria for evaluating the data (CDC, 2009). The NHANES 2001–2002 survey provides the data of eight OH-PAHs. In the NHANES 2003–2004 survey, ten PAH metabolites were measured in urine samples. In this study, we selected eight OH-PAHs which were available in both data cycles. The eight OH-PAHs are: naphthalene metabolites (i.e. 1-hydroxynaphthalene (1-NAP) and 2-hydroxynaphthalene (2-NAP)); fluorene metabolites (i.e. 2-hydroxyfluorene (2-FLUO), and 3-hydroxyfluorene (3-FLUO)); phenanthrene metabolites (i.e. 1-hydroxyphenanthrene (1-PHEN), 2-hydroxyphenanthrene (2-PHEN), and 3-hydroxyphenanthrene (3-PHEN)); and pyrene metabolite (i.e. 1-hydroxypyrene (1-PYR)). Urinary creatinine-correction was applied to the data. Creatinine was measured in all urine samples through automated colorimetric determination on a Beckman synchron CX3 clinical analyzer (Beckman Instruments Inc., Brea, CA) at the University of Minnesota's Fairview Medical Center. The urinary OH-PAHs (ng/l) were divided by urinary creatinine (mg/dl), and expressed as nanograms per gram of creatinine (ng/g). The limits of detection and correlations between creatinine-corrected OH-PAHs were reported previously (Xu et al., 2010).

2.4. Covariates

All covariates, which potentially acted as confounders, were carefully selected based on the evidence from literature and the availability in the dataset. Information on cigarette smoking, alcohol consumption and diabetes mellitus were measured by self-report questionnaire. Subjects were categorized into three groups of cigarette smoking (never smoking, former smoker, and current smoker). Alcohol consumption was classified into three groups (non-drinker, moderate drinker, and heavy drinker). Subjects were classified as non-drinkers if they answered not to have at least 12 alcohol drinks in their entire lifetime. The amount of alcohol consumption was determined from self-reported number of days with alcohol drinking and the average number of drinks per day when they drank alcohol in the past 12 months. NHANES defined that one drink was equivalent to 10 g ethanol represented 12-oz of beer, 4-oz of water or 1-oz of liquor. Total alcohol consumption in the past 12 months was estimated by: the number of drinks on a drinking day × 10 g × the number of drinking days over the past 12 months. Moderate drinker was defined as 1–19 g of alcohol consumption and heavy drinker was defined as 20 g or greater of alcohol consumption in the past 12 months. Subjects were classified as having diabetes if they had ever been told