

# Environment-wide association study to identify novel factors associated with peripheral arterial disease: Evidence from the National Health and Nutrition Examination Survey (1999–2004)

Xiaodong Zhuang<sup>a, b, 1</sup>, Ao Ni<sup>c, 1</sup>, Lizhen Liao<sup>d</sup>, Yue Guo<sup>a, b</sup>, Wei Dai<sup>c</sup>, Yunxi Jiang<sup>c</sup>, Huimin Zhou<sup>a, b</sup>, Xun Hu<sup>a, b</sup>, Zhimin Du<sup>a, b</sup>, Xueqin Wang<sup>c, e, \*\*</sup>, Xinxue Liao<sup>a, b, \*</sup>

<sup>a</sup> Cardiology Department, First Affiliated Hospital of Sun Yat-Sen University, China

<sup>b</sup> Key Laboratory on Assisted Circulation, Ministry of Health, China

<sup>c</sup> Department of Statistical Science, School of Mathematics and Computational Science, Sun Yat-Sen University, China

<sup>d</sup> Department of Health, Guangdong Pharmaceutical University, Guangzhou Higher Education Mega Center, China

<sup>e</sup> Joint Institute of Engineering, Sun Yat-Sen University, Carnegie Mellon University, China

## ARTICLE INFO

### Article history:

Received 6 October 2017

Received in revised form

8 December 2017

Accepted 11 January 2018

Available online 12 January 2018

### Keywords:

Peripheral arterial disease

Environment-wide association study

Ankle-brachial index

Cross-sectional

## ABSTRACT

**Background and aims:** An environment-wide association study (EWAS) may be useful to comprehensively test and validate associations between environmental factors and peripheral arterial disease (PAD) in an unbiased manner.

**Methods:** Data from cross-sectional cohorts from the US National Health and Nutrition Examination Survey (1999–2004) were randomly 50:50 split into training set and testing set. A value of ankle-brachial index (ABI) <1.0 or >1.4 defined PAD. We performed multiple linear regression analyses associating each of the 417 environmental and self-reported factors with PAD in the training set (false discovery rate <5%). Significant findings were validated in the testing set ( $p < 0.05$ ) and entered into a logistic regression model with penalized likelihood based on the Akaike Information Criterion (AIC).

**Results:** Overall, 6819 participants >40 years old were included. The validated factors comprised positive associations with smoking-associated factors (cigarette smoker, family smoker and smoked >100 cigarettes, urinary cotinine), cadmium, urinary albumin, C-reactive protein, blood o-xylene and thyroxine 4, and inverse associations with  $\alpha$ -carotene and trans-/cis- $\beta$ -carotene for PAD. Finally, only 4 of these factors were nominally significant in the AIC-selected model: cadmium (OR 1.27, 95% CI 1.12–1.45), cis- $\beta$ -carotene (OR 0.81, 95% CI 0.72–0.91), CRP (OR 1.19, 95% CI 1.03–1.38) and urinary albumin (OR 1.20, 95% CI 1.04–1.38).

**Conclusions:** Our systematic evaluation provides new knowledge on the complex array of environmental correlates of PAD. These identified correlates need to be probed in further observational and interventional studies.

© 2018 Elsevier B.V. All rights reserved.

## 1. Introduction

Peripheral arterial disease (PAD) is characterized by flow limiting atherosclerosis in the muscular arteries of the lower

extremities [1]. Patients with PAD have 3- to 5-fold higher mortality risk compared with those without PAD [2]. The causes of PAD have been deemed multifactorial, with both hereditary and non-hereditary/environmental factors playing a putative role [3]. Environmental exposures, such as blood cadmium, lead, polychlorinated biphenyls, dietary nutrients and tobacco, have been shown to be associated with moderate to large increases in PAD [3–6]. However, these documented findings often test associations of single factors with PAD, which may lead to an incomplete understanding of or even misleading notions about possible risk factors.

\* Corresponding author. The First Affiliated Hospital of Sun Yat-sen University, China.

\*\* Corresponding author. Department of Statistical Science, School of Mathematics and Computational Science, Sun Yat-Sen University, China.

E-mail addresses: [wangxq@mail.sysu.edu.cn](mailto:wangxq@mail.sysu.edu.cn) (X. Wang), [liaoxx@mail.sysu.edu.cn](mailto:liaoxx@mail.sysu.edu.cn) (X. Liao).

<sup>1</sup> These authors contributed equally to this work.

Environment-wide association study (EWAS), a study design analogous to the genome-wide association study (GWAS), has been proposed to search for and analytically validate environmental factors associated with complex diseases [7–11]. The advantage of this approach is that variables are examined using a systematic approach, thus avoiding selective reporting bias, while controlling for the rate of false positives [11]. Previous studies have scanned for associations between environmental exposure, behavioral and clinical factors putatively correlated with health-related phenotypes and outcomes, such as type 2 diabetes, blood pressure, metabolic syndrome, and all-cause mortality [10–12].

Here, we extend the EWAS approach to evaluate multiple associations between a wide range of environmental exposure and PAD using datasets from the National Health and Nutrition Examination Survey (NHANES). We claim that such an approach can prioritize physiological, environmental and self-reported indicator factors for future investigation into the causal nature, if any, of identified novel associations.

## 2. Patients and methods

The analytic procedure is summarized in Fig. 1.

### 2.1. Study population

NHANES is a cross-sectional, biannual, representative health survey of the United States population [13]. We used data from three cohort surveys (1999–2000, 2001–2002, and 2003–2004). This cross-sectional dataset is comprised of health questionnaire, laboratory (i.e. urinary phthalates, blood lead, blood cadmium, urinary mercury), and clinical data using a multistage probability sampling design. Data was collected through in-person interviews, physical measurement at mobile examination centers and laboratory samples. Self-reported data were also collected for supplement intake, diabetes mellitus, or cardiovascular disease status, family history of hypertension, and fitness level coded as metabolic equivalent of task (MET) [13]. Protocol approval and written informed consent were obtained by the National Center for Health Statistics Institutional Review Board for participants >18 years of age and from the guardians of participants <18. All methods were

carried out in accordance with the approved guidelines. All survey and consent documents for NHANES were approved by the CDC Institutional Review Board.

### 2.2. Peripheral arterial disease

Ankle-brachial index (ABI) was measured in subjects >40 years of age. A specific protocol was used to measure ABI in NHANES 1999 to 2004. For ABI determination, systolic blood pressure was measured on the right arm (brachial artery) and both ankles (posterior tibial arteries) with a Doppler device, the Parks Mini-Laboratory IV, model 3100 (Parks Medical Electronics). If the participant had a condition that would interfere with blood pressure reading in the right arm, the left arm was used. Systolic blood pressure was measured twice at each site for participants 40–59 years of age and once at each site for participants >60 years of age. The average of the measurements was used to calculate ABI for each side. Consistent with current guidelines, a value of ABI <1.0 or >1.4 defined PAD [14].

### 2.3. Statistical analysis

All variables in our analysis were either continuous or discrete. We log transformed the continuous variables that had right-skewed distribution, then we z-standardized all continuous as previous described. We omitted those variables that have a small subsample size to guarantee enough sample size. As shown in Supplemental Table 1, we associated each of 417 environmental and self-reported factors with ABI using survey-weighted logistic regression model, while adjusting for age, sex, ethnicity, body measure index and SES level both in the training set and testing set. We conducted regression analysis and accounted for clusters pseudo-strata, pseudo-sampling units and participant weights to accommodate the complex sampling of the data.

To valid our result within the dataset, we did a random 50:50 spilt of the dataset into training set and testing set. In the training set, we used the Benjamin-Hochberg procedure to control the false discovery rate (FDR) at level 5%. We used this method to control the expected proportion of false discoveries under 5%. We deemed a factor tentatively validated if it achieved FDR <5% significance in the training set and nominal statistical significance in the testing set ( $p$  value < 0.05). For tentatively validated factors, we computed its odds ratio (OR) and 95% confidence interval (CI). We further analyzed the independent factors using a logistic regression model with penalized likelihood based on the Akaike Information Criterion (AIC).

We assessed the Spearman correlations among all validated factors and visualized these variables in a heat map. Hierarchical clustering algorithm was used to arrange these factors in the heat map. The larger the correlation between a pair of variables, the closer in proximity they appeared in the heat map. All analyses were performed in R version 3.3.0 (R Foundation for Statistical Computing).

## 3. Results

Overall, 6819 participants >40 years old were followed in the 1999–2000 ( $n = 2124$ ), 2001–2002 ( $n = 2498$ ) and 2003–2004 ( $n = 2197$ ) surveys. Table 1 describes the baseline and demographic characteristics of patients with or without PAD in the training and testing dataset. There were significant differences in baseline factors such as sex, age, race, socioeconomic status, and comorbidity between the two groups. PAD occurred in higher age, more female and lower SES level in all cohorts ( $p < 0.05$ , two-sided  $t$ -test). Furthermore, there were significantly more patients with coronary

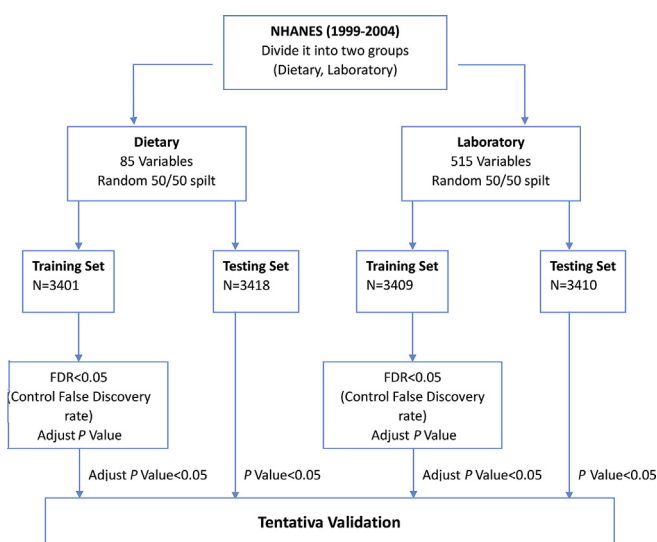


Fig. 1. Procedure to systematically associate environmental factors with peripheral arterial disease.

Download English Version:

<https://daneshyari.com/en/article/8657015>

Download Persian Version:

<https://daneshyari.com/article/8657015>

[Daneshyari.com](https://daneshyari.com)