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# Asymptomatic polyvascular disease and the risks of cardiovascular events and all-cause death

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ABSTRACT

*Background and aims:* Atherosclerosis is a diffuse and systemic disease. We aimed to assess prevalence and outcome of extracoronary polyvascular disease (polyVD) in the asymptomatic Chinese community population.

*Methods:* A random sample of 5440 participants aged 40 years or older were enrolled in the Asymptomatic Polyvascular Abnormalities Community Study from 2010 to 2011. Intracranial artery stenosis, extracranial artery stenosis, and lower extremity artery disease were detected by transcranial Doppler and duplex sonography, and by calculating the ankle brachial index. The study endpoints included the first occurrence of stroke, myocardial infarction (MI) and all-cause death.

*Results:* PolyVD (two or three affected vascular territories) was found in 3.0% of the participants, and was significantly higher in men (4.3%). Over a median follow-up of 4.1 years, we identified a total of 247 events (4.7%), including 83 strokes (68 ischemic), 45 MIs and 134 all-cause deaths. After adjusting for age, gender and other potential confounders, we found a significant increase in risk of major cardiovascular events as well as all-cause death in participants with polyVD. In multivariate Cox regression analyses, the adjusted hazard ratios (HR) (95% confidence interval, CI) for the composite of stroke, MI and all-cause death for single and poly-vascular disease (compared with 0 vascular disease) increased from 1.58 (1.19–2.12) to 1.95 (1.26–3.03). Similarly, the adjusted HR (95% CI) for all-cause death for single and polyvascular disease increased from 1.53 (1.03–2.29) to 2.22 (1.27–3.86).

*Conclusions:* PolyVD significantly increased the risk of major cardiovascular events and all-cause death in the asymptomatic community population. Performing invasive screening tests for polyVD is useful in the high-risk asymptomatic population.



## 1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of death and disability [1]. Considering that the prevention of CVD is less costly than treating its complications, the identification of subclinical disease in the asymptomatic phase is necessary [2,3]. It is well known that atherosclerosis has a common pathogenesis, and simultaneously affects multiple circulatory regions. Patients with symptomatic carotid artery atherosclerosis have a 30% and 20% co-

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prevalence of coronary artery disease (CAD)and lower extremity artery disease (LEAD), respectively [4]. The Reduction of Atherothrombosis for Continued Health (REACH) Registry has highlighted the role of atherosclerosis as a systemic disease with manifestations in multiple vascular beds, and shown that the patients had a poorer prognosis than those with just one territory affected [5]. Polyvascular disease (polyVD) is defined as the presence of more than one affected vascular bed [6,7]. However, different combinations were made in different studies, such as: CAD, cerebrovascular disease, LEAD, diseases of the aorta, etc. [6–9] The Carotid-Femoral Ultrasound Morphology and Cardiovascular Events (CAFES-CAVE) study showed that only scanning the carotid or the femoral artery predicted 15% and 13% fewer evesnts, respectively, than examining both territories in a 10-year follow-up, which showed the clinical value of a multiterritorial vascular evaluation [10]. Previous studies detected a high prevalence of polyVD and found that patients with polyVD had a markedly higher event rate than patients with atherosclerosis affecting only one arterial bed [5–8,11–13]. However, these studies mainly focused on patients with established atherothrombotic disease or risk factors. Coronary heart disease predominates in the Western population, whereas stroke is the dominant type of cardiovascular disease in the Asian population [14]. The European Society of Cardiology (ESC) Guidelines and the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guidelines on peripheral artery diseases paid more attention to non-coronary atherosclerosis, including extracranial carotid and vertebral, abdominal aortic, mesenteric, renal, and upper and lower extremity arteries [4,15,16]. However, the prevalence and outcome of polyVD in the asymptomatic community population, especially extracoronary vascular abnormalities and in the Chinese, are not well understood.

## 2. Materials and methods

### 2.1. Study design and population

Data were collected from the Asymptomatic Polyvascular Abnormalities Community study (APAC) [17], a community-based, prospective study investigating the epidemiology of asymptomatic polyvascular abnormalities in Chinese adults, including asymptomatic intracranial artery stenosis (ICAS), extracranial artery stenosis (ECAS) and LEAD. The APAC cohort was a subpopulation of the Kailuan study [18–21], described previously, which was an ongoing prospective cohort study conducted from 2006 in the Kailuan (Group) Co. Ltd in Tangshan city, a large and littoral modern city located in the southeast Beijing. From June 2010 to June 2011, a total of 7000 participants aged ≥40 years were randomly sampled from our reference population of 101,510 participants in the Kailuan study by using an age- and gender-stratified random sampling method. A total of 5816 participants eventually provided the informed consent and completed the baseline survey. A total of 376 participants were excluded, according to the inclusion criteria: recruited in the APAC study. During the baseline survey, all the participants had undergone a questionnaire assessment, clinical, laboratory, transcranial Doppler (TCD), and duplex sonography examinations. We excluded 216 participants because of missing ankle-brachial index (ABI) values, leaving 3134 men and 2090 women in the final statistical analysis. The APAC study was performed according to the guidelines of the Helsinki Declaration and was approved by the ethics committees of the Kailuan General Hospital and the Beijing Tiantan Hospital.

### 2.2. Assessment of polyVD

#### 2.2.1. Assessment of ICAS

Two experienced neurologists, who were blinded to the baseline information of the participants, completed TCD examinations using portable machines (Nicolet/EME Company, Germany). ICAS was diagnosed according to the peak systolic flow velocity in terms of published criterion [22]. The stenotic arteries were defined as: >140 cm per second (cm/s) for the middle cerebral artery, >120 cm/s for the anterior cerebral artery, >100 cm/s for the posterior cerebral artery and vertebra-basilar artery, and >120 cm/s for the siphon internal carotid artery. Presence of turbulence or musical sound, whether the abnormal velocity was segmental and the age of patients was also taken into account. Cerebral arteries that could not be insonated because of poor temporal acoustic windows were regarded as non-stenotic.

#### 2.2.2. Assessment of ECAS

All the participants underwent a bilateral carotid sonography including common carotid artery, internal carotid artery, external carotid artery, vertebral artery and subclavian artery, using a professional duplex sonography (Philips iU-22 ultrasound system, Philips Medical Systems, Bothell, WA, USA). ECAS was defined as a common or extracranial internal carotid artery stenosis, or an extracranial vertebral artery stenosis. The severity of stenosis was graded as <50%,50–69%, >69% and occlusion, according to recommendations from the Society of Radiologists in Ultrasound Consensus Conference [23].

#### 2.2.3. Assessment of LEAD

The ABI was calculated as the ratio of the ankle to the brachial systolic blood pressure. The bilateral dorsalis pedis, posterior tibial artery, and brachial artery systolic pressures were recorded, which were measured using a portable Doppler device (Hokanson MD6 Doppler with MD6VR Chart Recorder; Bellevue, WA, USA) after a 10-min rest in the supine position. The ABI was calculated at each side by dividing the higher value of the dorsalis pedis and posterior tibial artery systolic pressures by the higher value of the brachial artery systolic pressures in both arms. We used the lower ABI value for analysis. According to the 2011 ACCF/AHA guideline [16], a cutoff point of ABI ≤ 0.90 was considered abnormal.

#### 2.2.4. Assessment of potential covariates at baseline

Data on demographic information (including age, sex, household income, education, lifestyle, etc.) were collected using standardized questionnaires by our trained investigators, as described in previous studies [17,19]. Hypertension was defined as the presence of a history of hypertension, or receiving antihypertensive medication, or a systolic blood pressure of ≥ 140 mmHg, or a diastolic blood pressure of ≥ 90 mmHg. Diabetes mellitus was defined as a self-reported history, currently treated with insulin or oral hypoglycemic agents, or a fasting plasma glucose level ≥ 126 mg/dL. Hyperlipidemia was defined as a history, the current use of lipid-lowering medicine, or a total cholesterol level of ≥ 220 mg/dL or triglycerides of ≥ 150 mg/dL or low-density lipoprotein ≥ 160 mg/dL.

### 2.3. Follow-up and outcome assessment

Participants were followed up by face-to-face interviews at every 2-year routine medical examination until 31 December 2014 or to the event of interest or death. Trained physicians who were blinded to the baseline data performed the follow-ups. For the