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Comparative mortality according to peripheral artery disease and coronary heart disease/stroke in the United States

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ABSTRACT

Background and aims: A recent trial reported that patients with peripheral artery disease (PAD) without coronary heart disease or stroke (CHD/stroke) had worse prognosis than those with CHD/stroke without PAD. However, community-based data are lacking. The purpose of this study was to compare mortality according to the status of PAD and CHD/stroke in the general population.

Methods: In 6780 participants (aged ≥40 years) from the National Health and Nutrition Examination Surveys 1999–2004, we compared mortality risk according to PAD (ankle-brachial index ≤0.9) and CHD/stroke (self-report) at baseline using the Kaplan-Meier method and multivariable Cox models accounting for sampling weights.

Results: The prevalence of having both PAD and CHD/stroke was 1.6%. The prevalence of PAD without CHD/stroke and CHD/stroke without PAD was 4.1% and 8.5%, respectively (85.8% without PAD or CHD/stroke). Over a median follow-up of 12.8 years, 21.2% died. Individuals with both PAD and CHD/stroke had the worst survival (25.5% at 12 years). Those with PAD without CHD/stroke had the second worst prognosis (47.7%), followed by those with CHD/stroke without PAD (53.2%) and those without CHD/stroke or PAD (87.2%). Adjusted hazard ratio of mortality was 2.70 (95% CI, 2.07–3.53) for PAD with CHD/stroke, 1.81 (1.54–2.12) in CHD/stroke without PAD, and 1.68 (1.35–2.08) in PAD without CHD/stroke *vs.* no CHD/stroke or PAD.

Conclusions: In the US adults, PAD contributed to increased mortality in persons with and without CHD/stroke. The prognosis of PAD without CHD/stroke was no better than that of CHD/stroke without PAD. These results suggest the importance of recognizing the presence of PAD in the community.

1. Introduction

Lower-extremity peripheral artery disease (PAD) is often recognized as the third major atherosclerotic disease following coronary heart disease and stroke [1]. However, it is not necessarily clear what makes PAD "third." For example, the prevalence is estimated to be higher for PAD than stroke in the US (8–10 million *vs.* 7 million adults) [2,3]. In terms of their prognostic impact, a recent report from the FOURIER trial testing a PCSK9 inhibitor found that patients with PAD but without myocardial infarction or stroke (MI/stroke) had worse prognosis than those with MI/stroke but without PAD [4]. Specifically, the cumulative incidence of major adverse cardiovascular events over 2.2 years in the placebo arm was 10.3% in PAD without MI/stroke and 7.6% in MI/stroke without PAD. Similar results have been shown in a few other clinical studies [5,6]. However, these studies are based on clinical diagnosis of PAD (i.e., symptoms or signs of PAD or low ankle-brachial index [ABI] according to clinical indication). Since most patients with PAD do not have typical symptoms and PAD is often underdiagnosed, it is uncertain whether this observation holds in the general population. Therefore, using data collected in the 1999–2004 National Health and Nutrition Examination Survey (NHANES), we sought to compare the mortality risk according to PAD, defined as ABI ≤0.9, in the presence and absence of prevalent coronary heart disease or stroke (CHD/stroke) among US middle-aged and older adults.

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Table 1
Baseline characteristics of US adults aged 40 years or older by status of PAD and CHD/stroke, 1999–2004, weighted.

Characteristic	No CHD/stroke or PAD	PAD without CHD/stroke	CHD/stroke without PAD	PAD and CHD/stroke
No. of participants (unweighted)	5539	406	679	156
Age, years	54.7 (0.21)	67.0 (0.88)	64.4 (0.62)	70.7 (1.04)
Female, %	51.3 (0.8)	63.7 (3.0)	40.8 (2.6)	40.3 (5.6)
Race/ethnicity				
White, %	81.1 (1.6)	80.4 (2.4)	87.8 (1.4)	82.6 (3.2)
Black, %	8.9 (0.9)	13.9 (2.4)	7.2 (0.9)	12.3 (2.5)
Hispanic, %	10.1 (1.5)	5.7 (1.7)	5.0 (1.3)	5.1 (2.2)
Smoking status				
Never smoker, %	42.7 (1.1)	36.0 (3.3)	29.5 (2.4)	16.4 (3.7)
Former smoker, %	43.9 (1.1)	47.0 (3.6)	57.5 (2.5)	63.4 (4.7)
Current smoker, %	13.4 (0.8)	17.0 (2.0)	13.0 (2.0)	20.2 (4.9)
Diabetes, %	10.1 (0.5)	20.5 (2.6)	23.1 (1.9)	38.2 (5.3)
Systolic blood pressure, mmHg	126.6 (0.40)	139.2 (1.60)	130.6 (1.04)	141.7 (2.33)
Diastolic blood pressure, mmHg	74.1 (0.26)	67.3 (0.96)	69.4 (0.76)	65.3 (1.34)
Total cholesterol, mmol/L	5.4 (0.02)	5.4 (0.07)	5.1 (0.06)	5.3 (0.16)
HDL cholesterol, mmol/L	1.4 (0.01)	1.4 (0.02)	1.3 (0.02)	1.2 (0.04)
LDL cholesterol, mmol/L[a]	3.3 (0.03)	3.2 (0.09)	3.0 (0.06)	3.0 (0.12)
eGFR, mL/min/1.73 m [2]	94.6 (0.35)	84.4 (1.37)	81.8 (0.96)	67.7 (2.67)
Anti-hypertensive medication use, %	27.8 (0.9)	52.9 (3.3)	71.7 (2.8)	78.8 (4.5)
Statin use, %	11.0 (0.6)	21.6 (2.8)	45.1 (2.5)	54.7 (5.3)

Values indicate mean (SE) or proportion (SE).
CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAD, peripheral artery disease; SE, standard error.
[a] LDL cholesterol was available only in 3074 participants with fasting blood sample.

2. Patients and methods

2.1. Study population

NHANES is a periodic cross-sectional survey that uses a stratified and multi-stage probability sampling scheme to assess a nationally representative sample of US civilian non-institutionalized population on various health and nutritional outcomes [7]. Since 1999, NHANES has become a continuous program consisting of health interviews and physical examination in a two-year cycle. The survey protocol was approved by the institutional review board of the National Center for Health Statistics; all study participants provided written informed consent. Between 1999 and 2004, NHANES measured ABI among participants aged ≥40 years. Among 9970 participants aged ≥40 years in NHANES 1999–2004, we excluded those with missing ABI values (n = 2641), missing information on the status of CHD/stroke (n = 67), and missing covariates (n = 1829), leaving the final study sample of 6780. As anticipated, participants who were included in the study tended to have a healthier risk factor profile than those who were excluded from the study (Supplementary Table 1). For example, participants in the study were less likely to smoke or have diabetes and more likely to have lower systolic blood pressure than those not in the study. Conversely, lipid profiles, kidney function, and the proportion of statin use were largely similar.

2.2. Status of PAD and CHD/stroke

The presence of PAD was defined as ABI ≤0.9 in either leg. [8] Systolic blood pressures were measured on the right brachial artery and bilateral posterior tibial arteries using an 8.1 MHz Doppler probe [9]. Systolic blood pressures on each site were measured twice among participants aged 40–59 years and once among participants aged ≥60 years. ABI was calculated using the mean posterior tibial systolic blood pressure on each side, dividing by the mean brachial systolic pressure. A history of CHD/stroke was assessed based on self-report of prior CHD or stroke with the following questions: "Has a doctor … ever told you that you had coronary heart disease?" and "Has a doctor … ever told you that you had a stroke?". A history of heart attack ("Has a doctor … ever told you that you had a heart attack?") was similarly evaluated and considered as a history of MI.

2.3. Outcomes

Outcomes of interest were all-cause mortality and cardiovascular mortality after the baseline examination through December 31, 2015. To determine mortality status, NHANES 1999–2004 was linked to the National Death Index. Cardiovascular mortality was defined using the International Statistical Classification of Diseases, 10th Revision (ICD-10) when the underlying cause of death in the linked mortality file was listed as heart diseases (ICD-10 codes I00–I09, I11, I13, I20–I51) or cerebrovascular diseases (ICD-10 codes I60–I69). Participants not matched with the mortality database were assumed to be alive.

2.4. Covariates

Age, sex, race/ethnicity (White, Black, or Hispanic), smoking status (never, former, or current), and current use of anti-hypertensive medication or statin (yes or no) were based on self-report. The history of diabetes (yes or no) was defined by a self-reported history of diabetes, fasting glucose ≥7 mmol/L, or hemoglobin A1C ≥ 6.5%. Systolic blood pressure in our study was calculated by averaging the second and third measurements with a mercury sphygmomanometer [10]. Total cholesterol was measured in a series of enzymatic reactions that hydrolyze cholesteryl esters and oxidize the 3-OH group of cholesterol; high-density lipoprotein (HDL) cholesterol was measured by the heparin-manganese precipitation method technique [11]. Serum creatinine was chemically measured via kinetic alkaline picrate [12], and estimated glomerular filtration rate (eGFR) was calculated with the CKD-EPI equation [13].

2.5. Statistical analysis

All statistical analyses incorporated the survey weights to account for the complex NHANES sampling design. Baseline characteristics were compared across the four cross-categories by the presence and absence of PAD and CHD/stroke.

We first estimated the survival among those four cross-categories by PAD and CHD/stroke status using the Kaplan-Meier method and compared them using a log-rank test. We used three Cox proportional hazards models to evaluate the impact of potential confounding: Model 1 was unadjusted; Model 2 was adjusted for age, sex, and race/ethnicity;

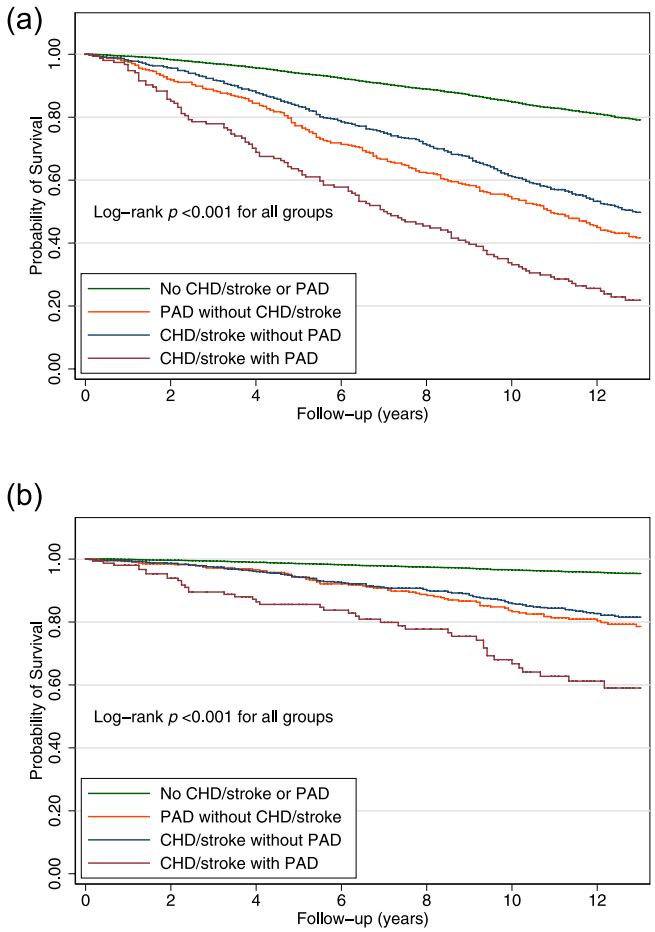

Fig. 1. Weighted survival estimates by the status of PAD and CHD/stroke.
(A) All-cause mortality. (B) Cardiovascular mortality. CHD, coronary heart disease; PAD, peripheral artery disease.

and Model 3 included all variables in Model 2 plus smoking status, history of diabetes, systolic blood pressure, anti-hypertensive medication use, statin use, total and HDL cholesterols, and eGFR.

We conducted sensitivity analyses to explore the robustness of our findings. We first conducted subgroup analyses by age, sex, and race/ethnicity. We then restricted CHD to MI and repeated our analysis. Since a previous study demonstrated high prevalence of PAD in this range of ABI, indicating incompressible calcified ankle arteries [14], we also explored an alternative definition of PAD including ABI >1.4 in addition to ABI ≤0.9. All analyses were performed using Stata, version 15.1 (StataCorp, College Station, TX), and a *p*-value <0.05 was considered statistically significant.

3. Results

The weighted mean age was 56.2 years, and the weighted proportion of Whites, Blacks, Hispanics was 81.6%, 9.0%, and 9.4%, respectively. The weighted prevalence of having both PAD and CHD/stroke was 1.6%. The weighted prevalence of PAD without CHD/stroke and CHD/stroke without PAD was 4.1% and 8.5%, respectively, and 85.8% of US adults aged 40 years or older did not have either PAD or CHD/stroke. US adults with PAD and CHD/stroke tended to be older and have poorer risk factor profile (e.g., higher systolic blood pressure, higher prevalence of diabetes, and lower kidney function) than the other three groups (Table 1). In addition, adults with PAD (regardless of CHD/stroke status) were

Table 2
Weighted hazard ratios (95%CI) of mortality by status of PAD and CHD/stroke.

Characteristic	No CHD/stroke or PAD	PAD without CHD/stroke	CHD/stroke without PAD	PAD and CHD/stroke
All-cause mortality				
No. of deaths/N (unweighted)	1277/5539	249/406	362/679	123/156
Model 1	1 (Reference)	4.40 (3.61–5.35)	3.55 (2.94–4.29)	9.30 (7.13–12.14)
Model 2	1 (Reference)	1.90 (1.56–2.32)	1.81 (1.54–2.12)	3.17 (2.43–4.14)
Model 3	1 (Reference)	1.68 (1.35–2.08)	1.81 (1.54–2.12)	2.70 (2.07–3.53)
Cardiovascular mortality				
No. of deaths/N (unweighted)	253/5539	66/406	107/679	43/156
Model 1	1 (Reference)	5.96 (4.27–8.30)	5.69 (4.11–7.87)	21.12 (14.86–30.03)
Model 2	1 (Reference)	2.54 (1.77–3.66)	2.73 (1.98–3.76)	6.83 (4.70–9.91)
Model 3	1 (Reference)	2.11 (1.48–3.01)	2.32 (1.75–3.08)	4.49 (3.10–6.50)

CHD, coronary heart disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; PAD, peripheral artery disease.
Model 1 was unadjusted; Model 2 was adjusted for age, sex, and race/ethnicity; Model 3 was further accounted for smoking status, total and HDL cholesterols, diabetes, eGFR, anti-hypertensive use, statin use, and systolic blood pressure.

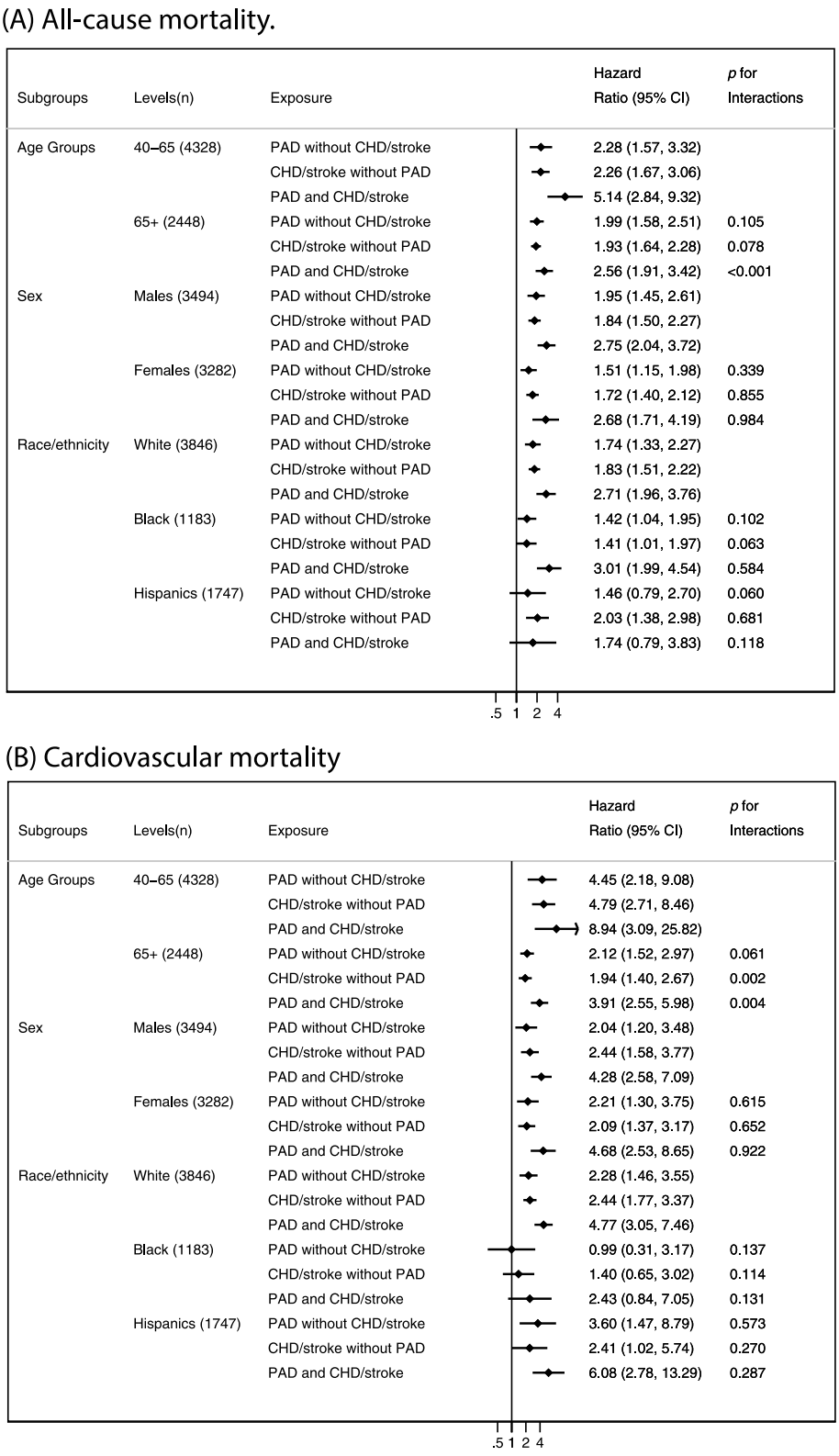

Fig. 2. Weighted adjusted hazard ratios (95%CI) of mortality by status of PAD and CHD/stroke across demographic subgroups.
(A) All-cause mortality. (B) Cardiovascular mortality. CHD, coronary heart disease; PAD, peripheral artery disease. Model was adjusted for age, sex, race/ethnicity, smoking status, total and HDL cholesterols, diabetes, eGFR, antihypertensive use, statin use, and systolic blood pressure (i.e., Model 3 in Table 2).

more likely to be older, females, Blacks, current smokers, and have higher systolic blood pressure compared to those without PAD. Fewer adults with PAD without CHD/stroke were taking anti-hypertensive medications and statin, compared with those with CHD/stroke without PAD or those with PAD and CHD/stroke. Nonetheless, only approximately half of participants with CHD/stroke were taking statins at baseline.

Over 16.8 years of follow-up (median 12.8 years [IQI, 11.2–14.7]),

2011 participants died (21.2% of the weighted study population), and 23.3% had cardiovascular disease as an underlying cause of death. Individuals with PAD and CHD/stroke had the worst survival (25.5% at 12 years), whereas those without CHD/stroke or PAD had the best survival (87.2%) (Fig. 1A). When we compared the remaining two groups, adults with PAD without CHD/stroke had worse survival than those with CHD/stroke without PAD (47.7% *vs.* 53.2%). The pattern was generally similar for cardiovascular mortality (Fig. 1B), although the separation in the survival curves between participants with PAD without CHD/stroke and those with CHD/stroke without PAD appeared less evident than all-cause mortality.

The general patterns remained consistent after adjusting for potential confounders (Table 2). Specifically, individuals with PAD and CHD/stroke had an elevated risk of all-cause mortality (hazard ratio of 2.70 [95%CI 2.07–3.53]) in Model 3. In this Model, those with CHD/stroke without PAD and those with PAD without CHD/stroke demonstrated similar mortality risk (hazard ratio 1.81 [95% CI 1.54–2.12] and 1.68 [95% CI 1.35–2.08], respectively). Hazard ratios were consistently greater for cardiovascular mortality than all-cause mortality in each of these three groups, with the highest hazard ratio seen in participants with PAD and CHD/stroke (4.49 [95% CI, 3.10–6.50] in Model 3). Again, the hazard ratios were similar between those with CHD/stroke without PAD (2.32 [95% CI, 1.75–3.08] in Model 3) and those with PAD without CHD/stroke (2.11 [95% CI, 1.48–3.01] in Model 3). We confirmed that PAD *vs.* no PAD conferred a significantly higher risk of mortality regardless of the presence or absence of CHD/stroke (Supplementary Table 2).

The pattern of the highest risk in individuals with PAD and CHD/stroke followed by similar risk between those with PAD without CHD/stroke and those with CHD/stroke without PAD was consistent across demographic subgroups by age, sex, and race/ethnicity (Fig. 2). More specifically, significant interactions were seen for age, with stronger associations for both all-cause and cardiovascular mortality in younger *vs.* older populations. The results were similar when we restricted CHD to MI (Supplementary Table 3, Supplementary Table 4, and Supplementary Fig. 1). The addition of ABI >1.4 to the definition of PAD did not materially alter our results (Supplementary Table 5 and Supplementary Fig. 2).

4. Discussion

In this study using data from NHANES, US adults aged 40 years or older with both PAD and CHD/stroke (accounting for 1.6% of the population) had the worst prognosis (12-year survival of 25.5%), and those with neither of CHD/stroke or PAD (85.8% of adults) had the best prognosis (12-year survival of 87.2%). When we compared the remaining two groups with either PAD or CHD/stroke, we found a similar or poorer prognosis among individuals with PAD without CHD/stroke (4.1% of adults) than those with CHD/stroke without PAD (8.5% of adults) (12-year mortality of 47.7% *vs.* 53.2%, respectively). The associations were overall consistent after adjustment for potential confounders, across demographic subgroups, and for all-cause mortality and cardiovascular mortality.

Our results regarding the comparable prognostic values of PAD *vs.* CHD/stroke are generally consistent with a few previous clinical studies, including a recent secondary analysis from FOURIER [4–6]. Nonetheless, there are a few unique aspects of our study. First, our study is nationally representative and generalizable to non-institutionalized US adults aged 40 or older [15,16]. Second, the ABI was obtained on all eligible study participants, but not due to clinical indications. Thus, our study should include less severe PAD compared to the previous clinical studies. Third, we confirmed generally similar patterns across key demographic factors. Finally, we evaluated long-term risk (median of 12.8 years of follow-up) as compared to a median follow-up of 1–6 years in those previous studies.

Possible mechanisms for the similar or potentially greater prognostic impact of PAD over CHD/stroke may include differences in the risk factor profiles for these three major atherosclerotic diseases. For example, smoking and diabetes are well-known risk factors of PAD and increase the risk of cardiovascular and non-cardiovascular diseases (e.g., cancer and end-stage kidney disease) [1,17,18]. This may be in line with our observation that the mortality difference between PAD without CHD/stroke *vs.* CHD/stroke without PAD was more evident for all-cause mortality than for cardiovascular mortality. Also, our observation may be due to limited use of preventive therapy among individuals with PAD compared to those with CHD/stroke [19]. The exact reasons behind inadequate attention to patients with PAD among healthcare providers are not fully clear, but this seems to reflect low awareness of PAD among providers [20] and the perception that heart diseases are more life-threatening than leg diseases [21]. Nonetheless, the results remained consistent even after accounting for these potential confounders of smoking status, diabetes, and preventive therapies in our study, suggesting the involvement of other mechanisms. For example, individuals with PAD may have overall poor prognosis since they tend to have systemic atherosclerosis [22,23], which makes their clinical management complex. Also, they are shown to have reduced physical function and activity [8,24,25].

The concept of "polyvascular disease" (atherosclerosis affecting two or more vascular beds) [26] has implications on intensive secondary prevention of atherosclerotic disease. There are novel antithrombotic and lipid-lowering therapies (e.g., vorapaxar and PCSK9 inhibitors) that are effective, but expensive [4,26]. In this context, patients with "polyvascular disease" are at extremely high risk of adverse outcomes and thus important candidates for those novel therapies. Our finding of adults with PAD and CHD/stroke demonstrating worse prognosis than those with neither or either of PAD or CHD/stroke further supports the importance of "polyvascular disease."

Our findings have important clinical implications. First, our results suggest that PAD defined by a low ABI may be considered equivalent to self-reported history of CHD/stroke in terms of prognosis. PAD is often underappreciated especially compared to CHD/stroke in the medical profession and among the lay public [20,27]. Second, PAD adds prognostic information among those with a history of CHD/stroke as well. Although the screening of PAD using ABI among individuals without leg symptoms is still controversial [28], our results support the recommendation of ABI measurement among those with known atherosclerotic diseases in another vascular bed by the American Heart Association and the American College of Cardiology [3].

Several limitations of this study should be acknowledged. First, the definition of CHD/stroke was based on self-report. Second, ischemic leg pain and a clinical history of PAD were not collected in NHANES, and thus we cannot compare symptomatic *vs.* asymptomatic PAD. Third, ankle systolic blood pressure was based on bilateral posterior tibial arteries, whereas clinical guidelines of PAD recommend measurement of the dorsalis pedis arteries as well. Fourth, we did not have follow-up information on other pertinent clinical endpoints such as incident/recurrent CHD, stroke, or heart failure. Fifth, we excluded a number of participants due to lack of data. Nonetheless, the prevalence of cardiovascular disease in our study was similar to previous reports [29]. Also, it seems likely that our estimates are conservative by missing severe PAD cases with poor risk factor profiles. Finally, as true in any observation study, we cannot deny the possibility of residual confounding.

In conclusion, the presence of PAD, defined by a low ABI, contributed to significantly elevated mortality risk in US middle-aged and older adults regardless of the presence or absence of CHD/stroke. Persons with both PAD and CHD/stroke had the worst prognosis. Importantly, persons with PAD without CHD/stroke showed a similar or even worse prognosis than those with CHD/stroke without PAD. These results underscore the importance of recognizing the presence of PAD in the community, especially since PAD is often underrecognized, underdiagnosed, and undertreated.

CRediT authorship contribution statement

Kunihiro Matsushita: has contributed to, Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing, Supervision. **Yumin Gao:** has contributed to, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Yingying Sang:** has contributed to, Formal analysis, Writing – review & editing, Visualization. **Shoshana H. Ballew:** has contributed to, Writing – original draft, Writing – review & editing. **Maya Salameh:** has contributed to, Writing – review & editing. **Matthew Allison:** has contributed to, Writing – review & editing. **Elizabeth Selvin:** has contributed to, Writing – review & editing. **Josef Coresh:** has contributed to, Writing – review & editing.

Declaration of competing interests

K.M. received research funding from NHLBI and a personal fee from Fukuda Denshi outside of the submitted work. Other authors did not have any relevant conflicts to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2022.04.029.

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