American Heart Association.

Lifetime Risk of Lower-Extremity Peripheral Artery Disease Defined by Ankle-Brachial Index in the United States

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Background—There are no available lifetime risk estimates of lower-extremity peripheral artery disease (PAD).

Methods and Results—Using data from 6 US community-based cohorts and the vital statistics, we estimated the prevalence and incidence of PAD, defined as an ankle-brachial index < 0.90, at each year of age from birth to 80 years for white, black, and Hispanic men and women. Then, we used Markov Monte Carlo simulations in a simulated cohort of 100 000 individuals to estimate lifetime risk of PAD. On the basis of odds ratios of PAD for traditional atherosclerotic risk factors (eg, diabetes mellitus and smoking), we developed a calculator providing residual lifetime risk of PAD. In an 80-year horizon, lifetime risks of PAD were 30.0% in black men and 27.6% in black women, but ≈19% in white men and women and ≈22% in Hispanic men and women. From another perspective, 9% of blacks were estimated to develop PAD by 60 years of age, while the same proportion was seen at ≈70 years for whites and Hispanics. The residual lifetime risk within the same race/ethnicity varied by 3.5- to 5-fold according to risk factors (eg, residual lifetime risk in 45-year-old black men was 19.9% when current smoking, diabetes mellitus, and history of cardiovascular disease were absent versus 70.4% when all were present).

Conclusions—In the United States, ≈30% of blacks are estimated to develop PAD during their lifetime, whereas the corresponding estimate is ≈20% for whites and Hispanics. The residual lifetime risk within the same race/ethnicity substantially varies according to traditional risk factors. (***J Am Heart Assoc***. 2019;8:e012177. DOI: 10.1161/JAHA.119.012177.)

Key Words: epidemiology • peripheral artery disease • risk factor • risk score

Lifetime risk is useful for communicating long-term risk and estimating the future burden of disease in populations.[1–5] Lifetime risk estimation of coronary heart disease and stroke is recommended in the American Heart Association and the American College of Cardiology guidelines for guiding preventive therapies.[6,7] However, to our knowledge, there are no available estimates of lifetime risk of lower-

extremity peripheral artery disease (PAD), despite its impact on prognosis,[8] leg amputation,[9] and physical function.[10] Here, using data from 6 US community-based cohorts with over 35 000 unique participants, we estimated lifetime risk of PAD by sex and among 3 racial/ethnic groups (whites, blacks, and Hispanics). Subsequently, we extended the lifetime risk estimations by age and other traditional atherosclerotic risk factors, which would complement lifetime risk prediction of coronary disease and stroke in the American Heart Association/American College of Cardiology guidelines[6,7] and facilitate personalized and comprehensive cardiovascular risk discussion between healthcare providers and patients.[6,11]

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Accompanying Data S1 through Data S4, Tables S1 through S5, and Figures S1 through S3 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012177

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Methods

This study was approved by the institutional review board for use of deidentified data at the Johns Hopkins Bloomberg School of Public Health (Baltimore, MD), and the need for informed consent was waived. Each participating cohort has its own policy for data sharing, but some of their data are publicly available (the National Health and Nutrition Examination Survey [NHANES] through the Centers for Disease

Clinical Perspective

What Is New?

- In blacks, ≈30% of men and women were estimated to develop peripheral artery disease (PAD) during their lifetime, whereas in whites and Hispanics the corresponding estimate is ≈20%.
- From another perspective, blacks reached a 10% lifetime risk for PAD ≈10 years earlier than whites and Hispanics.
- Current and former smoking, diabetes mellitus, and a history of other cardiovascular disease were particularly potent predictors of developing PAD, contributing to ≈5-fold gradient of residual lifetime risk and ≈10-fold gradient of the probability of prevalent PAD at a given age, sex, and race/ethnicity.

What Are the Clinical Implications?

- Although major guidelines for PAD did not specify black race as a risk factor of PAD, our results suggest the importance for healthcare providers to keep in mind this disproportional risk of PAD in blacks.
- Risk calculators for the lifetime risk of PAD as well as prevalent PAD have been developed from this study, which may contribute to comprehensive cardiovascular risk assessment and inform targeted PAD screening.

Control and Prevention's website[12] and other cohorts through BioLINCC[13]).

Lifetime Risk Estimation

There are 2 main approaches to estimate lifetime risk in the literature: (1) estimating long-term cumulative incidence from a survival analysis of individuals[14–16] and (2) estimating lifetime risk using Monte Carlo simulations with state transition probabilities based on a Markov chain model.[1,2] The former approach may sound more intuitive than the latter, but because there are few cohort studies with lifelong follow-up, the former approach often needs to stack cumulative incidences from different risk sets with different age categories. For example, to obtain lifetime risk from the age of 40 in a cohort with an age range of 40 to 80 years and follow-up of 20 years, cumulative incidence before and after the age of 60 years should rely on younger and older study populations, respectively, which potentially induces some biases (eg, birth cohort effects). Also, the former approach is likely to be particularly suboptimal for clinical conditions without evident signs or symptoms, as incidences may not be appropriately captured in any cohort studies. This issue is especially relevant to PAD because the vast majority of disease is asymptomatic or accompanied by atypical leg symptoms.[17] Also, very few cohort studies have regularly

repeated measurement of ankle-brachial index (ABI) in a relatively short elapsed time to capture asymptomatic cases to minimize the number of losses to follow-up or deaths between repeated ABI measurements. Thus, we estimated the lifetime risk of PAD using the Monte Carlo simulations approach.[2]

A Markov chain model was constructed to simulate progression of an initially PAD free individual of a given baseline age, sex, and race/ethnicity through the mutually exclusive states of no PAD, PAD, and death, with PAD and death treated as "absorbing states" (once entered unable to leave) (Data S1). State transition probabilities of interest were (1) the probability of developing PAD (I_{PAD}) and (2) the probability of dying prior to the development of PAD (Q_{noPAD}). Details for the calculations of each state transition probability are provided subsequently in the section "State Transition Probabilities and Data Sources" below as well as in Data S1. Using these state transition probabilities, Monte Carlo simulations were performed 100 000 times from the age of 0 through 80 years with a cycle length of 1 year, which is equivalent to a simulated cohort of 100 000 individuals of a specified baseline age, sex, and race with a lifetime horizon capped at 80 years. All analyses were performed by Stata 14 (StataCorp LP, College Station, TX).

State Transition Probabilities and Data Sources

Q_{noPAD} (1-year probability of dying among people free of PAD of a given age, sex, and race) was calculated from age-, sex-, and race/ethnicity-specific estimates of annual mortality in the overall population (ie, populations with and without PAD), the prevalence of PAD, and hazard ratios for mortality associated with PAD. This approach is based on the fact that annual overall mortality can be viewed as a weighted average of the 1-year probability of dying among people with PAD and that of those without PAD.[2] Annual probabilities of death for the US population by each year of age, sex, and race/ethnicity (whites, blacks, and Hispanics) were based on the National Vital Statistics Report.[18] The prevalence of PAD according to ABI <0.90[19,20] was based on data from a total of 6 US community-based cohorts (5 cohorts with ABI data included in the Cardiovascular Lifetime Risk Pooling Project,[21] namely, the ARIC [Atherosclerosis Risk in Communities] study,[22] the CHS [Cardiovascular Health Study],[23] the FHS [Framingham Heart Study],[24] the FOF [Framingham Offspring study], and the MESA [Multi-Ethnic Study of Atherosclerosis],[25] as well as NHANES 1999–2004).[26] Data collection in each study was conducted according to a standardized protocol as previously reported,[22–25] and details of how ABI was measured in each cohort are summarized in Data S2. The relative risk of mortality for PAD versus no PAD was also obtained from pooled data from these 6 US community-based cohorts.

I_{PAD} (the probability of developing PAD at a given age) was estimated from age-, sex-, and race/ethnicity-specific estimates of annual mortality in the overall population, Q_{noPAD} (detailed above), age-, sex-, and race/ethnicity-specific prevalence of no PAD (ie, 1- the prevalence of PAD). This approach is based on the fact that the prevalence of no PAD at age x+1 is determined by 3 elements, the prevalence of no PAD at age x (denominator) and 2 types of exits from no PAD, annual incidence of PAD during age x or mortality among no PAD during age x (ie, Q_{noPAD}). Data sources for these parameters were the same as those noted above for Q_{noPAD}. More details about state transition probabilities are provided in Data S1.

Estimating the Prevalence of PAD

Logistic regression models with age, sex, and race/ethnicity as independent variables were used to estimate the prevalence of PAD. To improve the precision of age-, sex-, and race/ethnicity-specific estimates of PAD prevalence, we used the pooled data of the 6 US cohort studies (indicators of 6 cohorts were included in logistic models).[2] Because NHANES is most representative of US populations among the 6 cohorts (although data were somewhat sparse in some age and race/ethnic groups), we combined the odds of PAD in a base case of 70-year-old white men in NHANES and odds ratios for age, sex, and race/ethnicity from the pooled data to estimate the prevalence of PAD for each year of age among sex and race/ethnicity groups (white men and women, black men and women, and Hispanic men and women). In this step, we used sample weights in NHANES. We also incorporated significant product terms between age, race/ethnicity, and sex.

Estimating Relative Risk of Mortality for PAD Versus No PAD

The relative risk of mortality for PAD (ABI <0.90) versus no PAD (ABI ≥0.90) was obtained from pooled data from the 6 US community-based cohorts using stratified Cox proportional hazards models. Cox models were adjusted for sex and race/ethnicity and incorporated interaction terms between PAD and age with splines (knots at age 65 years). Again, indicator variables for 6 cohorts were included in regression models.

Residual Lifetime Risk by Age and Traditional Atherosclerotic Risk Factors

Lifetime risk estimates from a given age (ie, residual lifetime risk) can be viewed as a weighted average of residual lifetime risk of subgroups determined by combinations of the presence and absence (or higher and lower values if continuous factors) of traditional risk factors at that given age. Using sample weights and actual values of traditional atherosclerotic risk factors in NHANES, as well as odds ratio of PAD for traditional atherosclerotic risk factors from the pooled data of 6 studies, we estimated residual lifetime risk by combinations of age and traditional atherosclerotic risk factors. More details can be found in Data S3.

Logistic regression models to estimate odds ratios of PAD in the pooled data of the 6 US cohort studies included diabetes mellitus, smoking (both current and former), systolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, and a history of coronary heart disease or stroke as well as age, sex, race/ethnicity, and study indicators.

Results

Study Characteristics

A total of 38 154 participants were included from the 6 cohorts, of whom 2517 participants (6.6%) had PAD based on an ABI <0.90. Whites and blacks were included in 4 cohorts: ARIC, CHS, MESA, and NHANES (Table 1). Hispanics were represented in 2 cohorts, MESA and NHANES. The mean age ranged from 55 to 80 years across the cohorts. Compared with cohorts with a lower average age, cohorts with an older average age tended to have a less favorable risk factor profile (eg, higher blood pressure and prevalence of diabetes mellitus). The prevalence of current smokers was highest in ARIC (26%) and lowest in FHS (6.7%). The prevalence of PAD varied from 3.8% in MESA to 21% in FHS. Generally consistent across cohorts, a history of coronary heart disease and stroke as well as most traditional atherosclerotic risk factors (ie, ever smokers, low high-density lipoprotein cholesterol, and diabetes mellitus) were more prevalent in men than in women (Table S1).

Estimates of PAD Prevalence and Mortality Risk Associated With PAD

Pooled results from logistic regression models confirmed age as a strong predictor of prevalent PAD, with an odds ratio of 1.56 (95% CI, 1.50–1.61) per 5-year increment (Table S2). At 65 years of age, women had slightly higher odds of having ABI <0.90 than men (odds ratio, 1.24 [95% CI, 1.12–1.38]), and this sex-difference was slightly but significantly attenuated with older age (as represented by odds ratio of 0.90 [per 5-year increment] for the product term of female and age). Compared with whites, blacks had >2-fold higher odds of having PAD (eg, 2.16 [95% CI, 1.86–2.52] for black men versus white men), without any difference by age. Hispanics had significantly lower odds of PAD than whites, especially in middle age (eg, 0.76 [95% CI, 0.62–0.93] for men at 65 years

Table 1. Study Characteristics

	Study					
	ARIC (14 274)	CHS (5662)	FHS (597)	FOF (3520)	MESA (6772)	NHANES (7329)
Total of death, N (%)	4272 (30%)	4608 (81%)	430 (72%)	380 (12%)	1144 (17%)	1516 (21%)
Follow-up time (y), mean (SD)	18.4 (5.2)	13.1 (6.5)	9.1 (3.9)	10.3 (2.1)	12.4 (2.5)	9.0 (2.6)
Age (y), mean (SD)	55 (5.9)	72 (5.5)	80 (3.9)	58 (9.6)	62 (10)	60 (13)
Female sex, N (%)	7757 (54%)	3234 (57%)	376 (63%)	1870 (53%)	3573 (53%)	3581 (48%)
Race/Ethnicity, N (%)						
White	10 719 (75%)	4790 (85%)	597 (100%)	3520 (100%)	2614 (39%)	4092 (56%)
Black	3555 (25%)	837 (15%)	. . .	. . .	1868 (28%)	1361 (19%)
Hispanic	. . .	35 (0.62%)	. . .	. . .	2290 (34%)	1876 (26%)
Smoking status, N (%)						
Never	5863 (41%)	2615 (47%)	557 (93%)	2977 (85%)	3403 (50%)	3063 (42%)
Former	4699 (33%)	2369 (42%)	. . .	. . .	2489 (37%)	3292 (45%)
Current	3712 (26%)	678 (12%)	40 (6.7%)	543 (15%)	880 (13%)	967 (13%)
SBP (mm Hg), mean (SD)	121 (19)	136 (22)	143 (21)	128 (18)	126 (21)	132 (21)
Total cholesterol (mmol/L), mean (SD)	5.6 (1.1)	5.5 (1.0)	5.3 (1.0)	5.3 (1.0)	5.0 (0.9)	5.4 (1.1)
HDL cholesterol (mmol/L), mean (SD)	1.3 (0.4)	1.4 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.4 (0.4)
Diabetes mellitus, N (%)	1579 (11%)	837 (15%)	130 (22%)	336 (9.6%)	848 (13%)	1200 (16%)
History of CHD or stroke, N (%)	1796 (13%)	893 (16%)	136 (23%)	221 (6.3%)	5 (0.07%)	914 (13%)
ABI, mean (SD)	1.13 (0.14)	1.06 (0.18)	1.01 (0.21)	1.11 (0.12)	1.11 (0.12)	1.09 (0.16)
PAD (ABI <0.90), N (%)	634 (4.4%)	759 (13%)	124 (21%)	112 (3.2%)	255 (3.8%)	633 (8.6%)

ABI indicates ankle-brachial index; ARIC, Atherosclerosis Risk in Communities study; CHD, coronary heart disease; CHS, Cardiovascular Health Study; FHS, Framingham Heart Study; FOF, Framingham Offspring study; HDL, high-density lipoprotein; MESA, Multi-Ethnic Study of Atherosclerosis; NHANES, National Health and Nutrition Examination Survey; PAD, peripheral artery disease; SBP, systolic blood pressure.

of age versus white men), but this difference was attenuated at older ages (1.16 [95% CI, 1.06−1.27] for the product term of age and Hispanic ethnicity). Estimates of PAD prevalence were higher in blacks than the other 2 racial/ethnic groups in either sex at any age (Figure S1).

Pooled Cox models demonstrated a sex- and race/ethnicity-adjusted hazard ratio of 2.43 (95% CI, 2.18−2.72 at age of 65 years) for total mortality comparing PAD (ABI <0.90) versus no PAD (ABI ≥0.90) (Table S3). The strength of association was slightly attenuated in older age (13% [95% CI, 8−17%] smaller hazard ratio per 5 year older age above 65 years) (Table S3).

Lifetime Risk Estimates by Sex and Race/Ethnicity

Using estimates of PAD prevalence and relative risk of mortality for PAD in the prior section as well as national mortality data, we estimated Q_{noPAD} (1-year probability of dying among people of a given age, sex, and race/ethnicity and free of PAD) and I_{PAD} (the probability of developing PAD at a given age) at each age from birth to 80 years in each sex

and racial/ethnic group (Table S4). On the basis of these estimates, the lifetime risk estimate was highest in black men, at 30.0%, followed by 27.6% in black women (Figure). The lifetime risk estimate was similar in white men and women,
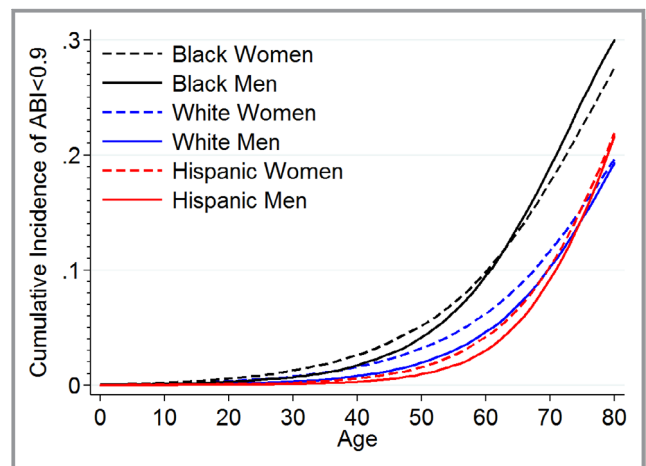

Figure. Lifetime cumulative incidence of PAD by race and sex. ABI indicates ankle-brachial index; PAD, peripheral artery disease.

with a lifetime risk of ≈19%, and Hispanic men and women, with a lifetime risk of ≈22%.

Residual Lifetime Risk of PAD by Traditional Risk Factors

Even after accounting for other traditional risk factors, age remained a strong predictor of PAD with an adjusted hazard ratio of 1.47 (95% CI, 1.43–1.52) (Table 2). Again, women had slightly higher odds of having an ABI <0.90 than men. Compared with whites, blacks had higher odds and Hispanics had lower odds of having PAD. All of the other traditional risk factors—diabetes mellitus, smoking (both current and former), systolic blood pressure, high-density lipoprotein cholesterol, total cholesterol, and a history of other cardiovascular disease—demonstrated significant associations with prevalent PAD.

On the basis of these estimates, we developed a calculator for residual lifetime risk as well as probability of prevalent PAD (http://ckdpcrisk.org/padrisk and every step is summarized in Data S4). According to this calculator, we observed a gradient of residual lifetime risk of PAD in the same race/ethnicity exceeding 3.5- to 5-fold according to traditional risk factors. For example, the residual risk varied from 19.9% to 70.4% in black men aged 45 years according to combinations of smoking, diabetes mellitus, and history of cardiovascular disease (Table 3). For an individual at age 65 years, because of the shorter duration to 80 years of age, the residual cumulative incidence was consistently lower than the scenario for an individual at age 45 years, at a given combination of traditional risk factors. Still, there was a 4- to 5.5-fold gradient of residual lifetime risk of PAD according to smoking,

Table 2. Adjusted Pooled OR of Having ABI <0.90

Variables	Pooled OR (95% CI)
Age, 5 y	1.47 (1.43, 1.52)
Female	1.31 (1.19, 1.44)
Black	1.65 (1.48, 1.84)
Hispanic	0.78 (0.64, 0.94)
Diabetes mellitus	1.54 (1.38, 1.71)
Former smoker	1.50 (1.34, 1.67)
Current smoker	3.09 (2.74, 3.49)
SBP, 20 mm Hg	1.27 (1.22, 1.32)
HDL cholesterol, 1 mmol/L	0.68 (0.60, 0.76)
Total cholesterol, 1 mmol/L	1.14 (1.09, 1.19)
History of coronary disease or stroke	2.01 (1.81, 2.24)

All variables were modeled simultaneously. ABI indicates ankle-brachial index; HDL, high-density lipoprotein; OR, odds ratio; SBP, systolic blood pressure.

diabetes mellitus, and a history of coronary disease or stroke within the same sex and race/ethnicity even in this scenario of a 65-year-old individual.

Predicting Prevalent PAD by Traditional Risk Factors

Using odds ratios of PAD according to traditional risk factors in Table 2 as well as the prevalence of PAD in the aforementioned base case in NHANES, we developed a calculator to predict the probability of having PAD as well. To cross-validate this approach, we split NHANES into 3 data sets (1999–2000, 2001–2002, and 2003–2004), developed a prediction model using 2 data sets, and compared predicted versus observed using the remaining data set. We indeed confirmed decent calibration (particularly in higher risk groups with all *P*>0.1 in the top 5 deciles for 3 cross-validation scenarios) and discrimination (cross-validated c-statistic=0.75) (Figure S2). To maximize available data for best predicting the probability of having PAD, the final model used the whole NHANES data, which demonstrated good calibration (χ^2 of 10.2 with *P*=0.35) and discrimination (c-statistic=0.77) (Figure S3). The variation of predicted probability of having PAD in several scenarios is shown in Table 4. The probability of having PAD within the same age, sex, and race/ethnicity varied by 6- to 10-fold by smoking status, diabetes mellitus, and a history of coronary disease or stroke (eg, predicted probability from 1.2% to 10.5% in 45-year-old black men).

Discussion

Using data from 6 US community-based cohorts, this study reported lifetime risk estimation of PAD. In blacks, ≈30% of men and women were estimated to develop PAD during their lifetime, whereas in whites and Hispanics the corresponding estimate is ≈20%. From another perspective, blacks reached a 10% lifetime risk for PAD 8 to 11 years earlier than whites and Hispanics. Women had a similar lifetime risk of PAD as men in all racial/ethnic groups. As anticipated, smoking (both current and former), diabetes mellitus, and a history of other cardiovascular disease were particularly potent predictors of developing PAD, contributing to an ≈5-fold gradient of residual lifetime risk and ≈10-fold gradient of the probability of prevalent PAD at a given age, sex, and race/ethnicity.

The higher lifetime risk of PAD in blacks compared with whites and Hispanics in our study is consistent with prevalence data shown in previous studies.[27,28] It is possible that this is partially explained by poor risk factor profiles in blacks compared with the other 2 groups, but this pattern

Table 3. Projected Residual Cumulative Incidence (%) of PAD in the United States Across Different Scenarios of Demographic and Clinical Factors

Demographic and clinical factors	Male	Female
Age 45 y		
Whites		
Nonsmoker		
No history of CHD or stroke		
No diabetes mellitus	11.3	13.4
Diabetes mellitus	16.4	19.2
History of CHD or stroke		
No diabetes mellitus	20.5	23.7
Diabetes mellitus	28.4	32.4
Current smoker		
No history of CHD or stroke		
No diabetes mellitus	28.4	32.4
Diabetes mellitus	37.8	42.4
History of CHD or stroke		
No diabetes mellitus	44.4	49.1
Diabetes mellitus	55.0	59.7
Blacks		
Nonsmoker		
No history of CHD or stroke		
No diabetes mellitus	19.9	17.7
Diabetes mellitus	27.6	24.8
History of CHD or stroke		
No diabetes mellitus	33.3	30.2
Diabetes mellitus	43.4	39.9
Current smoker		
No history of CHD or stroke		
No diabetes mellitus	43.4	39.9
Diabetes mellitus	54.1	50.5
History of CHD or stroke		
No diabetes mellitus	60.7	57.2
Diabetes mellitus	70.4	67.2
Age 65 y		
Whites		
Nonsmoker		
No history of CHD or stroke		
No diabetes mellitus	8.0	8.2
Diabetes mellitus	11.7	12.1
History of CHD or stroke		
No diabetes mellitus	14.8	15.3
Diabetes mellitus	21.1	21.7

Table 3. Continued

Demographic and clinical factors	Male	Female
Current smoker		
No history of CHD or stroke		
No diabetes mellitus	21.1	21.7
Diabetes mellitus	29.1	29.8
History of CHD or stroke		
No diabetes mellitus	35.0	35.8
Diabetes mellitus	45.3	46.1
Blacks		
Nonsmoker		
No history of CHD or stroke		
No diabetes mellitus	16.8	12.9
Diabetes mellitus	23.7	18.6
History of CHD or stroke		
No diabetes mellitus	29.0	23.0
Diabetes mellitus	38.5	31.5
Current smoker		
No history of CHD or stroke		
No diabetes mellitus	38.5	31.5
Diabetes mellitus	49.0	41.4
History of CHD or stroke		
No diabetes mellitus	55.8	48.1
Diabetes mellitus	66.0	58.7

Scenarios are all for a systolic blood pressure of 130 mmHg, high-density lipoprotein cholesterol of 50 mg/dL, and total cholesterol of 200 mg/dL. CHD indicates coronary heart disease; PAD, peripheral artery disease.

remained consistent even after accounting for key traditional atherosclerotic risk factors in the present study (Table 2) as well as in previous studies.[29] In this context, a recent study has demonstrated that socioeconomic factors such as education, household income, and neighborhood deprivation are associated with PAD risk beyond traditional risk factors.[30] Nonetheless, although major guidelines for PAD did not specify black race as a risk factor for PAD,[19] our results suggest the importance for healthcare providers to keep in mind this disproportional risk of PAD in blacks.

We observed a slightly higher prevalence of PAD in women than in men, particularly below 65 years of age (and similar lifetime risk of PAD between women and men). This may seem counterintuitive in light of epidemiology of other atherosclerotic diseases such as coronary disease, but several previous community-based studies report the same pattern for PAD prevalence.[27,31,32] Some reports suggest that this may be partially explained by shorter height in women than in men, potentially influencing ankle blood pressure.[33,34] Importantly, this cannot be simply interpreted as misclassification, as ABI

Table 4. Estimated Probability of Prevalent PAD (%) in the United States Across Different Scenarios of Demographic and Clinical Factors

Demographic and clinical factors	Male	Female
Age 45 y		
Whites		
Nonsmoker		
No history of CHD or stroke		
No diabetes mellitus	0.6	1.4
Diabetes mellitus	0.9	2.1
History of CHD or stroke		
No diabetes mellitus	1.2	2.7
Diabetes mellitus	1.8	4.1
Current smoker		
No history of CHD or stroke		
No diabetes mellitus	1.8	4.1
Diabetes mellitus	2.8	6.2
History of CHD or stroke		
No diabetes mellitus	3.6	8.0
Diabetes mellitus	5.5	11.8
Blacks		
Nonsmoker		
No history of CHD or stroke		
No diabetes mellitus	1.2	1.8
Diabetes mellitus	1.8	2.8
History of CHD or stroke		
No diabetes mellitus	2.4	3.6
Diabetes mellitus	3.6	5.5
Current smoker		
No history of CHD or stroke		
No diabetes mellitus	3.6	5.5
Diabetes mellitus	5.5	8.2
History of CHD or stroke		
No diabetes mellitus	7.1	10.4
Diabetes mellitus	10.5	15.2
Age 65 y		
Whites		
Nonsmoker		
No history of CHD or stroke		
No diabetes mellitus	2.7	4.3
Diabetes mellitus	4.1	6.4
History of CHD or stroke		
No diabetes mellitus	5.3	8.2
Diabetes mellitus	7.9	12.1

Table 4. Continued

Demographic and clinical factors	Male	Female
Current smoker		
No history of CHD or stroke		
No diabetes mellitus	7.9	12.1
Diabetes mellitus	11.7	17.5
History of CHD or stroke		
No diabetes mellitus	14.8	21.7
Diabetes mellitus	21.1	29.9
Blacks		
Nonsmoker		
No history of CHD or stroke		
No diabetes mellitus	6.6	6.9
Diabetes mellitus	9.8	10.3
History of CHD or stroke		
No diabetes mellitus	12.4	13.1
Diabetes mellitus	17.9	18.8
Current smoker		
No history of CHD or stroke		
No diabetes mellitus	17.9	18.8
Diabetes mellitus	25.1	26.2
History of CHD or stroke		
No diabetes mellitus	30.5	31.7
Diabetes mellitus	40.3	41.7

Scenarios are all for a systolic blood pressure of 130 mmHg, high-density lipoprotein cholesterol of 50 mg/dL, and total cholesterol of 200 mg/dL. CHD indicates coronary heart disease; PAD, peripheral artery disease.

<0.90 conferred a 2-fold higher risk of mortality as compared with the reference category of 1.1 to 1.2 in both men and women.[8] Nonetheless, as the American Heart Association called for action,[35] further studies are need for PAD in women, including investigations of its similar burden between men and women. In this context, it will be important to evaluate lifetime risk specifically for severe types of PAD requiring leg revascularization or amputation in both sexes.

There seem to be a few ways to use the risk calculators from this study. For example, our lifetime risk calculator can be complementary to the American Heart Association/American College of Cardiology lifetime risk calculator for coronary disease and stroke[7] and may contribute to comprehensive cardiovascular risk assessment. Importantly, the awareness of PAD is low, and most PAD patients do not have typical leg symptoms of intermittent claudication.[17] Also, diagnostic processes and signs/symptoms are unique for PAD (eg, leg examination, ABI measurement, and reduced leg pulse). Thus, identifying people at high lifetime risk of PAD may have implications on targeted patients' education about

manifestation and complications of PAD. The risk calculator for prevalent PAD may have implications for screening PAD. Although it is still under debate,[19,36] some guidelines recommend screening PAD using ABI among high-risk individuals.[19] Although those clinical guidelines empirically rely on age and the presence of a few key risk factors to identify "high-risk" populations for PAD (eg, all adults aged ≥65 years or people aged 50 to 64 years with any atherosclerotic risk factors[19]), our risk calculator for prevalent PAD will allow healthcare providers and patients to quantify the risk objectively on the basis of a combination of risk factors.

Although we tried to use the best readily available data in the United States, we need to acknowledge several limitations. First, most data were collected in the 1990s or early 2000s, and, unfortunately, few contemporary US community-based cohorts measured ABI in multiple racial/ethnic groups. Since a recent international study reported that the prevalence of PAD increased by 13% in high-income countries from 2000 to 2010,[32] our estimates may be conservative. On the other hand, the increase in prevalent PAD may be attributable to improved survival in people with PAD rather than an increased incidence, and thus a follow-up investigation with contemporary data would be important. Also, we cannot deny the possibility of birth cohort effects on prevalence of PAD. Second, we could not reliably estimate lifetime risk of PAD over the age of 80 years because of sparse data in this age range in our data sets (eg, NHANES coded all ages older than 80 as age 80). Given extending life expectancy in the United States, this is another element indicating that our estimates are likely to be conservative. Third, as anticipated from the literature,[37] the mortality rate in our cohorts tended to be lower than the mortality rate from vital statistics (Table S5). However, our lifetime risk estimation is based on the mortality rate from vital statistics and relative risk from 6 US cohorts. Of note, cardiovascular relative risk of many risk factors including ABI has been shown to be often consistent regardless of the baseline risk of study populations.[8,38] Fourth, we did not have systematic data regarding history of leg revascularization across cohorts, indicating some level of underestimation by not capturing some PAD cases with ABI >0.90 after vascular procedures. Fifth, a few cohorts did not have granular data of smoking status. Sixth, as true for almost any diagnostic tests, ABI is validated to diagnose PAD but is not perfect (sensitivity and specificity >90%–95% in various studies[39–42]). For example, a high ABI may mask PAD in some individuals.[43] Finally, although our data consisted of the 3 major racial/ethnic groups in the United States, data for other racial/ethnic groups were lacking.

In conclusion, ≈30% of blacks are estimated to develop PAD during their lifetime, whereas the estimate is ≈20% for whites and Hispanics. Unlike other atherosclerotic diseases, lifetime risk and the prevalence of PAD based on ABI <0.90 was similar in women and in men. Among traditional atherosclerotic risk factors, age, smoking, and diabetes mellitus as well as a history of coronary disease or stroke are confirmed to be potent predictors of PAD risk and contributed to substantial variation of lifetime risk of PAD within the same race/ethnicity.

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Disclosures

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SUPPLEMENTAL MATERIAL

Data S1. State transition probabilities.

Markov chain model used to simulate the progression of an individual free of peripheral artery disease (PAD) through death or the development of PAD.
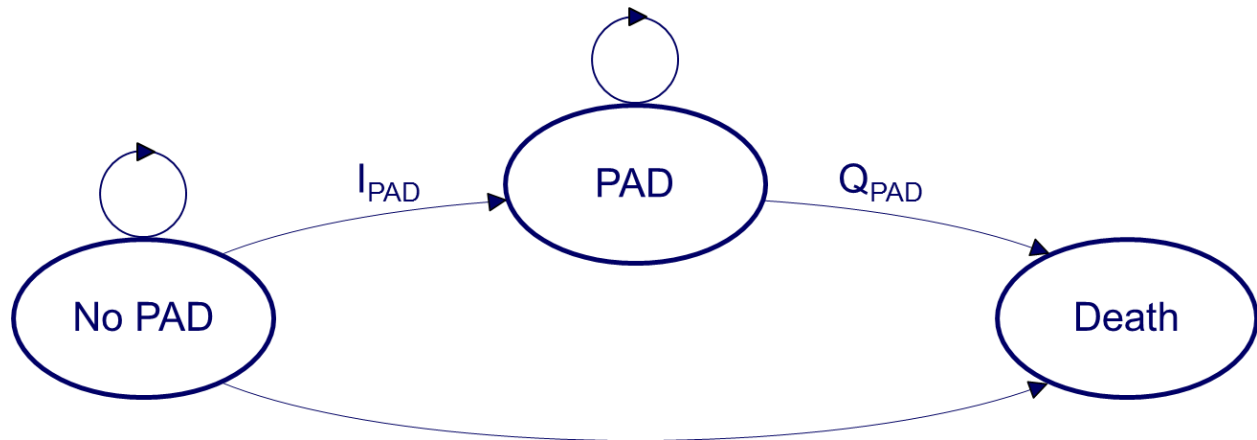
Terms of symbols in the formula

P_x --- prevalence of PAD at a given age, sex and race/ethnicity (from section "Estimating the prevalence of PAD")

P_{x+1} --- prevalence of PAD at the next year of age as for P1x (from section "Estimating the prevalence of PAD")

HR_x --- hazard ratios of mortality for PAD vs. no PAD at a given age, sex and race/ethnicity (from section "Estimating the relative risk of mortality for PAD vs. no PAD")

Q_x --- annual probability of death for the US population at a given age, sex and race/ethnicity (from National Vital Statistics Report)

Q_{0x} (Q_{noPAD}) --- 1-year probability of dying among persons free of PAD at a given age, sex and race/ethnicity

Q_{1x} (Q_{PAD}) --- 1-year probability of dying among persons with PAD at a given age, sex and race/ethnicity

RR_x --- risk ratios of mortality for PAD vs. no PAD at a given age, sex and race/ethnicity

I_x (I_{PAD}) --- the probability of developing PAD at a given age, sex race/ethnicity

Step 1: calculate Q_{0x}. This approach is based on the fact that annual overall mortality can be viewed as weighted average of 1-year probability of dying among persons with PAD and that of those without PAD

From Cox survival model

$Q_{1x} = 1 - (1 - Q_{0x})\; \wedge HR_x$ (1)

$RR_x = Q_{1x} / Q_{0x} = (1 - (1 - Q_{0x})\,{}^{\wedge}HR_x) / Q_{0x}$ (2)

$Q_x = (1 - P_x)\,Q_{0x} + P_x\,Q_{1x} = (1 - P_x)\,Q_{0x} + P1_x\,RR_x\,Q_{0x} = (1 - P_x + P_x\,RR_x)\,Q_{0x}$ (3)

$Q_{0x} = Q_x / (1 - P_x + P_x\,RR_x)$ (4)

Since we do not know RR_x, we used iterations to approximate RR_x.

From equation (2) above, the limit of RR_x of Q_{0x} as Q_{0x} approaches 0 equals HR_x. So we used HR_x as the beginning value of RR_x. During iterations, we first used equation (4) and RR_x from the previous iteration to get Q_{0x} of the current iteration. Then we used equation (2) to get RR_x of the current iteration. The iterations were stopped until the difference of Q_{0x} between current and previous iteration was less than 1E-8.
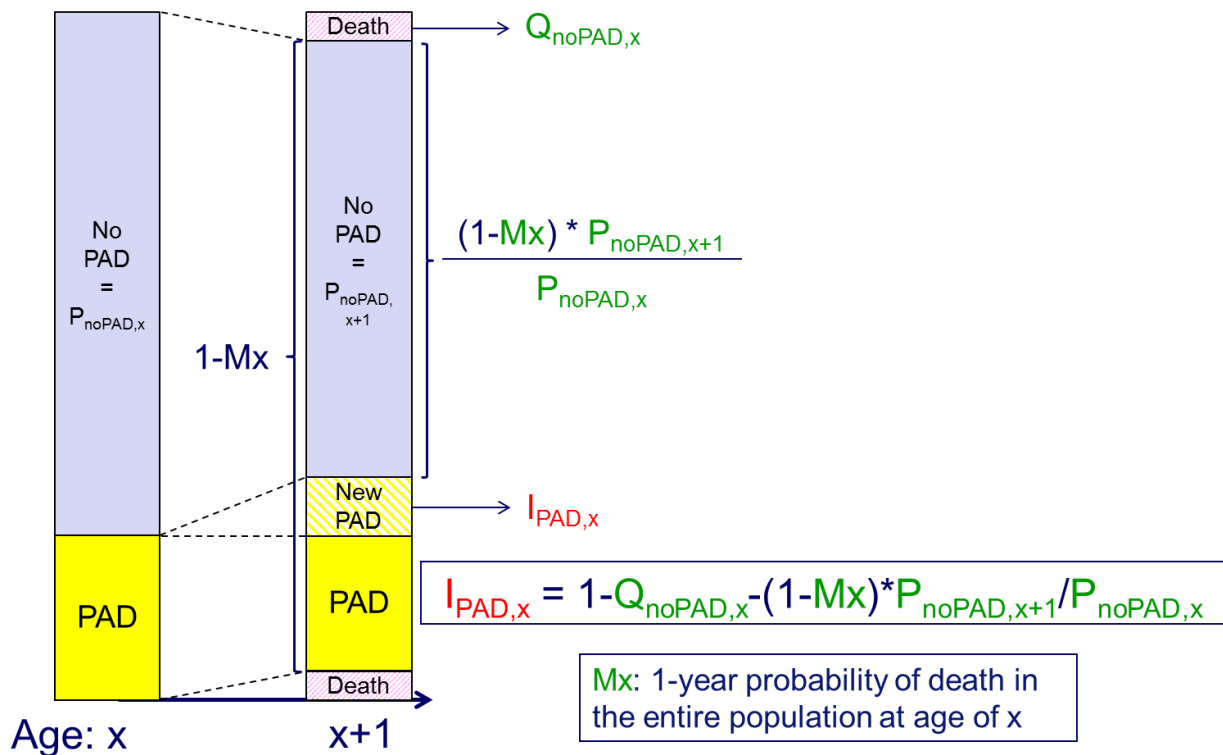
Step 2: calculate I_x. This approach is based on the fact that the prevalence of no PAD at age of x+1 is determined by four elements, the prevalence of no PAD at age of x, two types of exits from no PAD, annual incidence of PAD during age of x or mortality among no PAD during age of x, and annual mortality of the population.

$1 - P_{x+1} = (1 - P_x)\,(1 - I_x - Q_{0x}) / (1 - Q_x)$ (5)

$1 - I_x - Q_{0x} = (1 - P_{x+1})\,(1 - Q_x) / (1 - P_x)$ (6)

$I_x = 1 - Q_{0x} - (1 - P_{x+1})\,(1 - Q_x) / (1 - P_x)$ (7)

The scheme below depicts how we obtained $I_{PAD,x}$.

$$Q_{noPAD,x}$$

$$\frac{(1-Mx) * P_{noPAD,x+1}}{P_{noPAD,x}}$$

$$I_{PAD,x}$$

$$I_{PAD,x} = 1 - Q_{noPAD,x} - (1-Mx)*P_{noPAD,x+1}/P_{noPAD,x}$$

Mx: 1-year probability of death in the entire population at age of x

Data S2. Methods for measuring ABI in each cohort.

ARIC: The ABI was measured by Dinamap Model 1846 SX, an oscillometric device.[1] Ankle systolic blood pressure was measured a maximum of four times in a randomly selected single leg, and the last measurement was used for ABI. Brachial systolic blood pressure was measured twice, and the first measurement was used.

FHS and FOF: The ABI was measured using an 8-MHz Doppler probe and an ultrasonic Doppler flow detector (Parks Medical Electronics Inc, Shaw Aloha, Oregon).[2, 3] Systolic blood pressure was measured twice on both arms and both ankles. When the first two blood pressure values were different by >10 mmHg at any site, a third measurement was performed. When the posterior tibial pulse was not located, measurement was conducted at the dorsalis pedis artery. The ABI was calculated for each leg as the average ankle systolic blood pressure divided by the average systolic blood pressure of the higher arm.

MESA: The ABI was measured by a handheld Doppler instrument with a 5-MHz probe.[4] Systolic blood pressure was measured at the right and left brachial, dorsalis pedis, and posterior tibial arteries. The higher value of brachial artery pressure was used as the denominator of ABI. The higher pressure from dorsalis pedis or posterior tibial was used as the numerator of ABI for each leg, and the smaller value between right or left was recorded.

NHANES: Systolic blood pressure was measured on the right arm (left arm was used if there were any conditions on the right arm that would interfere with blood pressure measurement) and bilateral posterior tibial arteries.[5] The measurements were done twice among participants aged 40-59 years and once in participants aged 60 years or older. ABI was calculated for each leg by dividing the average systolic blood pressure in the ankle by the average blood pressure in the arm, and the smaller value was recorded.

Data S3. Residual lifetime cumulative incidence by traditional atherosclerotic risk factors.

Lifetime cumulative incidence estimates at a given age, sex and race/ethnicity can be viewed as a weighted average of residual lifetime risk of subgroups determined by combinations of the presence and absence (or higher and lower values if continuous factors) of traditional risk factors at that given age, sex and race/ethnicity. Using sample weights and actual values of traditional risk factors in NHANES, we first estimated lifetime cumulative incidence for a hypothetical person at a given age, sex and race/ethnicity, as well as traditional risk factors.

Terms of symbols in the formula

R_x --- Lifetime cumulative incidence estimates of PAD at a given age, sex and race/ethnicity (from section "Lifetime accumulative incidence estimation")

R_{x0} --- Lifetime cumulative incidence estimates of PAD at a given age, sex and race/ethnicity for a hypothetical person with given values of traditional risk factors (no diabetes, nonsmoker, systolic blood pressure 120 , high-density lipoprotein cholesterol 60mg/dL, total cholesterol 200 mg/dL and no history of CHD or stroke)

R_{xi} --- Lifetime cumulative incidence estimates of PAD at a given age, sex and race/ethnicity for a real individual in NHANES with actual values of traditional risk factors

OR_{xi} --- odds ratios of PAD for a real individual in NHANES compared to the hypothetical person at the same sex and race/ethnicity group and within 5 year of age (from section "Estimating relative risk of PAD for traditional risk factors", combined with difference between actual value of the individual and the given value of the hypothetical person for each risk factor as well as age)

W_{xi} --- sample weight for a real individual in NHANES at the same sex and race/ethnicity group and within 5 year of age

TW --- total sample weight for real individuals in NHANES at the same sex and race/ethnicity group and within 5 year of age

RR_{xi} --- risk ratios of PAD for a real individual in NHANES compared to the hypothetical person at the same sex and race/ethnicity group and within 5 year of age.

From logistic model

$$R_{xi} = R_{x0} OR_{xi} / (1 - R_{x0} + R_{x0} OR_{xi}) \quad (8)$$

$$RR_{xi} = R_{xi} / R_{x0} = OR_{xi} / (1 - R_{x0} + R_{x0} OR_{xi}) \quad (9)$$

$$R_x = \text{sum of i } (R_{xi} W_{xi} / TW) = \text{sum of i } (RR_{xi} R_{x0} W_{xi} / TW) = \text{sum of i } (RR_{xi} W_{xi}) R_{x0} / TW \quad (10)$$

$$R_{x0} = R_x TW / \text{sum of i } (RR_{xi} W_{xi}) \quad (11)$$

Since we do not know RR_{xi}, we used iterations to approximate RR_{xi}.

From equation (9) above, RR_{xi} approximately equals OR_{xi} when R_{x0} is very small. So we used OR_{xi} as the beginning value of RR_{xi}. During iterations, we first used equation (11) and RR_{xi} from the previous iteration to get R_{x0} of the current iteration. Then we used equation (9) to get RR_{xi} of the current iteration. The iterations were stopped until the difference of R_{x0} between current and previous iteration was less than 1E-8.

By using equation (9) above, we can estimate residual lifetime cumulative incidence for scenarios with combinations of any traditional risk factors.

Data S4. Project an Individual's residual cumulative incidence (%) of PAD in the United States.

Step 1: Calculate linear function (B) for individual participant

B = 0.1194242 × (SBP − 120) /10 − 0.3924322 × (HDLC − 1.5516) + 0.1301318 × (Tchol − 5.172) + 0.4291214 (if diabetes) + 0.4024582 (if former smoker) + 1.129064 (if current smoker) + 0.6998957 (if history of CVD)

Step 2: Use the Lifetime Risk (%) for given age, sex, and race x (Hx)

Age Group	White Man	White Woman	Black Man	Black Woman	Hispanic Man	Hispanic Woman
40-44	10.996	13.045	16.922	16.335	10.601	14.178
45-49	9.307	11.033	16.605	14.678	9.197	13.352
50-54	8.760	9.401	14.730	16.944	11.227	13.878
55-59	8.473	9.359	18.222	15.068	8.584	12.654
60-64	6.917	7.287	13.709	12.058	8.655	10.319
65-69	6.481	6.698	13.971	10.647	10.156	8.857
70-74	5.575	5.087	11.872	6.764	7.181	6.090
75-79	3.754	3.554	8.821	4.716	5.007	4.547

Step 3: Project residual cumulative incidence (%) for an individual

Residual cumulative incidence (%) = H_x × exp(B) / (100 + H_x × (exp(B) − 1)) × 100

Table S1. Baseline study characteristics by sex.

Male	Study					
	ARIC (6517)	**CHS (2428)**	**FHS (221)**	**FOF (1650)**	**MESA (3199)**	**NHANES (3748)**
Total of death - N (%)	2366 (36%)	2123 (87%)	173 (78%)	239 (14%)	653 (20%)	895 (24%)
Follow-up time (y) - Mean(SD)	18 (5.6)	12 (6.5)	8.4 (4.0)	10 (2.2)	12 (2.7)	8.8 (2.7)
Age (y) - Mean (SD)	55 (5.9)	73 (5.7)	79 (3.9)	59 (9.7)	62 (10)	60 (13)
Race/Ethnicity - N (%)						
White	5121 (79%)	2092 (86%)	221 (100%)	1650 (100%)	1255 (39%)	2124 (57%)
Black	1396 (21%)	319 (13%)	-	-	835 (26%)	691 (18%)
Hispanic	-	17 (0.70%)	-	-	1109 (35%)	933 (25%)
Smoking Status - N (%)						
Never	1798 (28%)	772 (32%)	212 (96%)	1408 (85%)	1296 (41%)	1020 (27%)
Former	2938 (45%)	1386 (57%)	-	-	1438 (45%)	2252 (60 %)
Current	1781 (27%)	270 (11%)	9 (4.1%)	242 (15%)	465 (15%)	473 (13%)
SBP (mmHg) - Mean (SD)	122 (18)	136 (21)	143 (22)	129 (17)	126 (19)	130 (19)
Total cholesterol (mmol/L) - Mean(SD)	5.5 (1.0)	5.1 (0.9)	5.0 (0.8)	5.1 (1.0)	4.6 (0.9)	5.3 (1.1)
HDL cholesterol (mmol/L) - Mean(SD)	1.1 (0.4)	1.2 (0.3)	1.1 (0.4)	1.1 (0.3)	1.2 (0.3)	1.2 (0.4)
Diabetes - N (%)	735 (11%)	416 (17%)	58 (26%)	195 (12%)	444 (14%)	659 (18%)
History of CHD or stroke - N (%)	878 (13%)	505 (21%)	74 (33%)	156 (9.5%)	3 (0.09%)	576 (15%)
ABI - Mean (SD)	1.16 (0.14)	1.08 (0.20)	1.04 (0.23)	1.14 (0.13)	1.14 (0.13)	1.11 (0.16)
PAD (ABI <0.90) - N (%)	220 (3.4%)	359 (15%)	48 (22%)	56 (3.4%)	121 (3.8%)	312 (8.3%)

Female	Study					
	ARIC (7757)	CHS (3234)	FHS (376)	FOF (1870)	MESA (3573)	NHANES (3581)
Total of death - N (%)	1906 (25%)	2485 (77%)	257 (68%)	141 (7.5%)	491 (14%)	621 (17%)
Follow-up time (y) - Mean(SD)	19 (4.8)	14 (6.3)	9.4 (3.8)	10 (1.9)	13 (2.3)	9.2 (2.5)
Age (y) - Mean (SD)	54 (5.9)	72 (5.4)	80 (3.9)	58 (9.5)	62 (10)	60 (13)
Race/Ethnicity - N (%)						
White	5598 (72%)	2698 (83%)	376 (100%)	1870 (100%)	1359 (38%)	1968 (55%)
Black	2159 (28%)	518 (16%)	-	-	1033 (29%)	670 (19%)
Hispanic	-	18 (0.56%)	-	-	1181 (33%)	943 (26%)
Smoking Status - N (%)						
Never	4065 (52%)	1843 (57%)	345 (92%)	1569 (84%)	2107 (59%)	2043 (57%)
Former	1761 (23%)	983 (30%)	-	-	1051 (29%)	1040 (29%)
Current	1931 (25%)	408 (13%)	31 (8.2%)	301 (16%)	415 (12%)	494 (14%)
SBP (mmHg) - Mean (SD)	120 (20)	137 (22)	143 (21)	126 (19)	127 (23)	133 (23)
Total cholesterol (mmol/L) - Mean(SD)	5.6 (1.1)	5.7 (1.0)	5.5 (1.0)	5.5 (1.0)	5.2 (0.9)	5.5 (1.0)
HDL cholesterol (mmol/L) - Mean(SD)	1.5 (0.4)	1.5 (0.4)	1.4 (0.4)	1.5 (0.4)	1.5 (0.4)	1.5 (0.4)
Diabetes - N (%)	844 (11%)	421 (13%)	72 (19%)	141 (7.5%)	404 (11%)	541 (15%)
History of CHD or stroke - N (%)	918 (12%)	388 (12%)	62 (16%)	65 (3.5%)	2 (0.06%)	338 (9.4%)
ABI - Mean (SD)	1.11 (0.14)	1.05 (0.15)	0.99 (0.19)	1.08 (0.10)	1.09 (0.11)	1.07 (0.15)
PAD (ABI <0.90) - N (%)	414 (5.3%)	400 (12%)	76 (20%)	56 (3.0%)	134 (3.8%)	321 (9.0%)

SD: standard deviation; SBP: systolic blood pressure; HDL: high-density lipoprotein; ABI: ankle-brachial index; PAD: peripheral artery disease

Table S2. Odds ratio of PAD (ABI <0.9) according to demographic factors from the pooled data of six US cohorts.

Demographic variables	Odds ratios for ABI<0.9
Age for White and Black male, per 5y	1.56 (1.50, 1.61)
Female at age 65 for Whites	1.24 (1.12, 1.38)
Black for male	2.16 (1.86, 2.52)
Hispanic at age 65 for male	0.76 (0.62, 0.93)
Age * female, per 5y	0.90 (0.86, 0.94)
Age * Hispanic, per 5y	1.16 (1.06, 1.27)
Female * Black	0.77 (0.63, 0.94)

All variables listed were modeled simultaneously.

Table S3. Sex- and race/ethnicity-adjusted hazard ratios (95% CIs) for mortality according to PAD (ABI <0.9) vs. no PAD (ABI ≥0.9)

Characteristic	HR (95% CIs)
Low ABI at age 65	2.43 (2.18, 2.72)
Low ABI * age with age<65, per 5y	1.09 (1.00, 1.18)
Low ABI * age with age≥65, per 5y	0.87 (0.83, 0.92)

All variables listed were modeled simultaneously.

Table S4. Estimated Q_{noPAD} (1-year probability of dying among persons of a given age, sex, and race/ethnicity and free of PAD) and I_{PAD} (the probability of developing PAD at a given age) at each age from birth to 80 years in each sex and racial/ethnic group.

	White men		White women		Black men		Black women		Hispanic men		Hispanic women	
Age	$Q_{noPAD,x}$	$I_{PAD,x}$	$Q_{noPAD,x}$	$I_{PAD,x}$	$Q_{noPAD,x}$	$I_{PAD,x}$	$Q_{noPAD,x}$	$I_{PAD,x}$	$Q_{noPAD,x}$	$I_{PAD,x}$	$Q_{noPAD,x}$	$I_{PAD,x}$
0	0.0060382	0.0000224	0.0049966	0.0000843	0.0139084	0.0000534	0.0114623	0.0001567	0.0060643	0.0000032	0.0050652	0.0000130
1	0.0004640	0.0000227	0.0003913	0.0000827	0.0007636	0.0000492	0.0005462	0.0001385	0.0004421	0.0000034	0.0003704	0.0000135
2	0.0002985	0.0000247	0.0002167	0.0000881	0.0004622	0.0000535	0.0003487	0.0001476	0.0002846	0.0000039	0.0001887	0.0000148
3	0.0002337	0.0000270	0.0001573	0.0000941	0.0003470	0.0000584	0.0003214	0.0001577	0.0001934	0.0000043	0.0001619	0.0000163
4	0.0001671	0.0000294	0.0001427	0.0001006	0.0003105	0.0000637	0.0002063	0.0001682	0.0001723	0.0000049	0.0001383	0.0000180
5	0.0001565	0.0000322	0.0001248	0.0001076	0.0002693	0.0000696	0.0001894	0.0001798	0.0001467	0.0000055	0.0001203	0.0000198
6	0.0001400	0.0000351	0.0001138	0.0001150	0.0002516	0.0000760	0.0001582	0.0001921	0.0001289	0.0000062	0.0001081	0.0000218
7	0.0001247	0.0000384	0.0001052	0.0001229	0.0002293	0.0000830	0.0001376	0.0002053	0.0001123	0.0000069	0.0001002	0.0000241
8	0.0001055	0.0000419	0.0000965	0.0001314	0.0001909	0.0000906	0.0001260	0.0002195	0.0000921	0.0000078	0.0000954	0.0000265
9	0.0000837	0.0000457	0.0000878	0.0001405	0.0001394	0.0000989	0.0001226	0.0002346	0.0000692	0.0000088	0.0000937	0.0000292
10	0.0000684	0.0000500	0.0000821	0.0001502	0.0000945	0.0001079	0.0001278	0.0002509	0.0000519	0.0000099	0.0000958	0.0000322
11	0.0000756	0.0000546	0.0000852	0.0001606	0.0000901	0.0001179	0.0001428	0.0002683	0.0000557	0.0000111	0.0001033	0.0000355
12	0.0001238	0.0000597	0.0001036	0.0001718	0.0001644	0.0001289	0.0001687	0.0002869	0.0000996	0.0000125	0.0001185	0.0000391
13	0.0002216	0.0000653	0.0001402	0.0001838	0.0003333	0.0001411	0.0002048	0.0003070	0.0001949	0.0000141	0.0001420	0.0000431
14	0.0003528	0.0000714	0.0001885	0.0001967	0.0005609	0.0001546	0.0002471	0.0003284	0.0003287	0.0000159	0.0001714	0.0000475
15	0.0004888	0.0000782	0.0002412	0.0002105	0.0007961	0.0001695	0.0002919	0.0003514	0.0004750	0.0000180	0.0002050	0.0000523
16	0.0006165	0.0000855	0.0002894	0.0002253	0.0010067	0.0001857	0.0003363	0.0003759	0.0006159	0.0000202	0.0002375	0.0000577
17	0.0007456	0.0000936	0.0003290	0.0002410	0.0012031	0.0002033	0.0003806	0.0004022	0.0007552	0.0000228	0.0002642	0.0000636
18	0.0008759	0.0001024	0.0003567	0.0002578	0.0013860	0.0002227	0.0004264	0.0004303	0.0008895	0.0000257	0.0002825	0.0000701
19	0.0010050	0.0001121	0.0003762	0.0002757	0.0015626	0.0002438	0.0004753	0.0004604	0.0010173	0.0000290	0.0002946	0.0000772
20	0.0011433	0.0001227	0.0003953	0.0002949	0.0017594	0.0002670	0.0005314	0.0004926	0.0011544	0.0000327	0.0003057	0.0000851
21	0.0012718	0.0001342	0.0004165	0.0003154	0.0019565	0.0002924	0.0005905	0.0005271	0.0012811	0.0000368	0.0003183	0.0000938
22	0.0013553	0.0001468	0.0004351	0.0003373	0.0020987	0.0003199	0.0006429	0.0005640	0.0013514	0.0000415	0.0003299	0.0001033
23	0.0013763	0.0001604	0.0004506	0.0003606	0.0021539	0.0003496	0.0006812	0.0006032	0.0013446	0.0000467	0.0003399	0.0001139
24	0.0013519	0.0001751	0.0004637	0.0003856	0.0021411	0.0003817	0.0007082	0.0006449	0.0012869	0.0000525	0.0003483	0.0001255
25	0.0013129	0.0001911	0.0004772	0.0004123	0.0021021	0.0004166	0.0007343	0.0006896	0.0012171	0.0000590	0.0003576	0.0001382
26	0.0012838	0.0002086	0.0004921	0.0004408	0.0020757	0.0004547	0.0007659	0.0007373	0.0011620	0.0000664	0.0003666	0.0001523
27	0.0012646	0.0002278	0.0005073	0.0004713	0.0020680	0.0004964	0.0008011	0.0007884	0.0011209	0.0000747	0.0003724	0.0001678
28	0.0012644	0.0002488	0.0005239	0.0005039	0.0020970	0.0005422	0.0008440	0.0008431	0.0011004	0.0000841	0.0003743	0.0001849

	White men		White women		Black men		Black women		Hispanic men		Hispanic women	
Age	$Q_{noPAD,x}$	$I_{PAD,x}$	$Q_{noPAD,x}$	$I_{PAD,x}$	$Q_{noPAD,x}$	$I_{PAD,x}$	$Q_{noPAD,x}$	$I_{PAD,x}$	$Q_{noPAD,x}$	$I_{PAD,x}$	$Q_{noPAD,x}$	$I_{PAD,x}$
29	0.0012809	0.0002718	0.0005439	0.0005388	0.0021585	0.0005925	0.0008969	0.0009017	0.0010957	0.0000946	0.0003752	0.0002037
30	0.0013052	0.0002969	0.0005700	0.0005762	0.0022380	0.0006475	0.0009625	0.0009645	0.0010937	0.0001065	0.0003758	0.0002244
31	0.0013319	0.0003243	0.0006035	0.0006162	0.0023173	0.0007077	0.0010386	0.0010319	0.0010919	0.0001198	0.0003822	0.0002472
32	0.0013633	0.0003543	0.0006420	0.0006590	0.0024199	0.0007736	0.0011237	0.0011041	0.0010792	0.0001348	0.0003976	0.0002723
33	0.0014067	0.0003872	0.0006875	0.0007048	0.0024507	0.0008447	0.0012012	0.0011811	0.0011309	0.0001518	0.0004378	0.0003002
34	0.0014546	0.0004231	0.0007357	0.0007538	0.0024994	0.0009226	0.0012825	0.0012634	0.0011744	0.0001710	0.0004881	0.0003308
35	0.0015152	0.0004623	0.0007896	0.0008063	0.0025566	0.0010076	0.0013684	0.0013515	0.0012266	0.0001925	0.0005467	0.0003647
36	0.0015917	0.0005053	0.0008520	0.0008626	0.0026413	0.0011009	0.0014700	0.0014460	0.0012897	0.0002168	0.0006083	0.0004020
37	0.0016831	0.0005525	0.0009244	0.0009229	0.0027590	0.0012032	0.0015956	0.0015477	0.0013744	0.0002441	0.0006733	0.0004431
38	0.0017931	0.0006041	0.0010105	0.0009876	0.0029212	0.0013156	0.0017535	0.0016574	0.0014851	0.0002750	0.0007402	0.0004884
39	0.0019260	0.0006607	0.0011116	0.0010570	0.0031279	0.0014393	0.0019419	0.0017756	0.0016183	0.0003099	0.0008113	0.0005384
40	0.0020736	0.0007227	0.0012201	0.0011315	0.0033660	0.0015750	0.0021443	0.0019025	0.0017709	0.0003493	0.0008882	0.0005935
41	0.0022445	0.0007908	0.0013391	0.0012113	0.0036306	0.0017240	0.0023579	0.0020387	0.0019347	0.0003936	0.0009758	0.0006543
42	0.0024567	0.0008657	0.0014791	0.0012971	0.0039327	0.0018876	0.0025970	0.0021853	0.0021018	0.0004436	0.0010788	0.0007214
43	0.0027111	0.0009481	0.0016388	0.0013895	0.0042697	0.0020675	0.0028596	0.0023431	0.0022656	0.0004999	0.0011998	0.0007955
44	0.0029929	0.0010388	0.0018088	0.0014885	0.0046392	0.0022649	0.0031371	0.0025125	0.0024302	0.0005633	0.0013354	0.0008773
45	0.0032796	0.0011380	0.0019808	0.0015945	0.0050127	0.0024808	0.0034143	0.0026937	0.0026051	0.0006348	0.0014803	0.0009675
46	0.0035701	0.0012466	0.0021511	0.0017077	0.0054195	0.0027179	0.0036944	0.0028875	0.0028008	0.0007154	0.0016308	0.0010670
47	0.0038829	0.0013658	0.0023230	0.0018289	0.0059230	0.0029806	0.0039956	0.0030958	0.0030221	0.0008064	0.0017885	0.0011767
48	0.0042294	0.0014969	0.0025008	0.0019586	0.0065616	0.0032736	0.0043302	0.0033203	0.0032787	0.0009093	0.0019546	0.0012977
49	0.0046108	0.0016412	0.0026893	0.0020976	0.0073193	0.0035996	0.0046969	0.0035623	0.0035729	0.0010254	0.0021313	0.0014311
50	0.0050250	0.0017997	0.0028966	0.0022470	0.0081400	0.0039596	0.0050937	0.0038230	0.0038966	0.0011567	0.0023275	0.0015784
51	0.0054540	0.0019737	0.0031166	0.0024071	0.0089777	0.0043546	0.0054976	0.0041021	0.0042487	0.0013048	0.0025373	0.0017408
52	0.0058863	0.0021641	0.0033389	0.0025784	0.0098475	0.0047887	0.0058881	0.0043992	0.0046412	0.0014723	0.0027448	0.0019196
53	0.0063126	0.0023721	0.0035593	0.0027612	0.0107327	0.0052643	0.0062480	0.0047139	0.0050751	0.0016617	0.0029394	0.0021160
54	0.0067439	0.0025997	0.0037875	0.0029569	0.0116324	0.0057851	0.0065891	0.0050478	0.0055457	0.0018756	0.0031267	0.0023317
55	0.0071995	0.0028493	0.0040285	0.0031665	0.0126175	0.0063601	0.0069414	0.0054048	0.0060732	0.0021177	0.0033222	0.0025692
56	0.0077006	0.0031239	0.0043064	0.0033925	0.0136499	0.0069919	0.0073299	0.0057884	0.0066381	0.0023913	0.0035436	0.0028310
57	0.0082524	0.0034261	0.0046479	0.0036379	0.0146019	0.0076739	0.0077575	0.0062010	0.0071853	0.0026989	0.0037959	0.0031199
58	0.0088623	0.0037590	0.0050702	0.0039056	0.0154138	0.0084032	0.0082455	0.0066470	0.0076792	0.0030435	0.0040906	0.0034389
59	0.0095266	0.0041256	0.0055632	0.0041969	0.0161333	0.0091859	0.0088041	0.0071303	0.0081361	0.0034297	0.0044293	0.0037913
60	0.0102477	0.0045293	0.0061153	0.0045131	0.0168518	0.0100342	0.0094446	0.0076552	0.0085940	0.0038633	0.0048068	0.0041803
61	0.0110167	0.0049731	0.0067012	0.0048541	0.0176850	0.0109664	0.0101553	0.0082236	0.0091131	0.0043522	0.0052209	0.0046094

	White men		White women		Black men		Black women		Hispanic men		Hispanic women	
Age	$Q_{noPAD,x}$	$I_{PAD,x}$	$Q_{noPAD,x}$	$I_{PAD,x}$	$Q_{noPAD,x}$	$I_{PAD,x}$	$Q_{noPAD,x}$	$I_{PAD,x}$	$Q_{noPAD,x}$	$I_{PAD,x}$	$Q_{noPAD,x}$	$I_{PAD,x}$
62	0.0118283	0.0054606	0.0073075	0.0052206	0.0186714	0.0119955	0.0109087	0.0088352	0.0097311	0.0049049	0.0056814	0.0050830
63	0.0126917	0.0059964	0.0079283	0.0056138	0.0198587	0.0131373	0.0116616	0.0094862	0.0105013	0.0055323	0.0061945	0.0056060
64	0.0136353	0.0065873	0.0085877	0.0060379	0.0212007	0.0143965	0.0124078	0.0101778	0.0114238	0.0062445	0.0067682	0.0061839
65	0.0147176	0.0072435	0.0093504	0.0065019	0.0226730	0.0157796	0.0132002	0.0109203	0.0124666	0.0070506	0.0074245	0.0068238
66	0.0160049	0.0079061	0.0102757	0.0069601	0.0243399	0.0170951	0.0141728	0.0116198	0.0136317	0.0079138	0.0081928	0.0074993
67	0.0174127	0.0086245	0.0112766	0.0074467	0.0259332	0.0184635	0.0152008	0.0123524	0.0148693	0.0088727	0.0090175	0.0082349
68	0.0188965	0.0093973	0.0123221	0.0079586	0.0273930	0.0198724	0.0163035	0.0131210	0.0161176	0.0099304	0.0098661	0.0090312
69	0.0204738	0.0102279	0.0134457	0.0084996	0.0287685	0.0213276	0.0175170	0.0139308	0.0173635	0.0110932	0.0107413	0.0098919
70	0.0221607	0.0111198	0.0146714	0.0090724	0.0300198	0.0228187	0.0187703	0.0147688	0.0186248	0.0123694	0.0116419	0.0108198
71	0.0241157	0.0120897	0.0161474	0.0096932	0.0314385	0.0243945	0.0200805	0.0156364	0.0199747	0.0137721	0.0126443	0.0118253
72	0.0264680	0.0131521	0.0178453	0.0103582	0.0334119	0.0261226	0.0217066	0.0165750	0.0214678	0.0153135	0.0138401	0.0129205
73	0.0291013	0.0142969	0.0197306	0.0110628	0.0357968	0.0279724	0.0236453	0.0175806	0.0231860	0.0170080	0.0153101	0.0141170
74	0.0319259	0.0155148	0.0217536	0.0118001	0.0388376	0.0299813	0.0258418	0.0186399	0.0251324	0.0188624	0.0170373	0.0154157
75	0.0349096	0.0168013	0.0239242	0.0125695	0.0424434	0.0321215	0.0282534	0.0197410	0.0271593	0.0208667	0.0188975	0.0168052
76	0.0381151	0.0181601	0.0263736	0.0133823	0.0460587	0.0342791	0.0307084	0.0208507	0.0294029	0.0230360	0.0208046	0.0182762
77	0.0418193	0.0196147	0.0291561	0.0142405	0.0501478	0.0365214	0.0336099	0.0220262	0.0320727	0.0253914	0.0229083	0.0198430
78	0.0461280	0.0211697	0.0324286	0.0151552	0.0546033	0.0388095	0.0369800	0.0232601	0.0353255	0.0279459	0.0253269	0.0215153
79	0.0511228	0.0228234	0.0361976	0.0161199	0.0592316	0.0410888	0.0400724	0.0244320	0.0392497	0.0307010	0.0281402	0.0232964
80	0.0564387	0.0245285	0.0402896	0.0171093	0.0641786	0.0433605	0.0437745	0.0256629	0.0436807	0.0336254	0.0312835	0.0251719

Table S5. 1-year probability of dying among those with ABI >0.9 by age categories.

Age, years	Q$_{noPAD,x}$ MCMC model	Mortality rate in cohort					
		ARIC	CHS	FHS	FOF	MESA	NHANES
White men							
45	0.0032795	0.0021880	0.0009498	0.0011324	0.0005746	0.0004181	0.0016187
55	0.0071989	0.0057350	0.0024921	0.0029707	0.0015080	0.0010976	0.0038198
65	0.0147150	0.0149888	0.0065306	0.0077816	0.0039548	0.0028795	0.0090004
75	0.0349024	0.0425772	0.0186995	0.0222554	0.0113516	0.0082735	0.0211321
White women							
45	0.0019808	0.0014211	0.0006168	0.0007354	0.0003731	0.0002715	0.0010181
55	0.0040288	0.0037273	0.0016188	0.0019298	0.0009793	0.0007128	0.0024036
65	0.0093520	0.0097574	0.0042450	0.0050592	0.0025695	0.0018705	0.0056688
75	0.0239289	0.0278543	0.0121811	0.0145066	0.0073849	0.0053795	0.0133401
Black men							
45	0.0050128	0.0031765	0.0013794			0.0006073	0.0025685
55	0.0126175	0.0083194	0.0036179			0.0015939	0.0060572
65	0.0226729	0.0216977	0.0065306			0.0028795	0.0142504
75	0.0424430	0.0612442	0.0270464			0.0119950	0.0333385
Black women							
45	0.0034142	0.0020636	0.0008958			0.0003944	0.0016158
55	0.0069412	0.0054094	0.0023504			0.0010352	0.0038130
65	0.0132003	0.0141417	0.0061600			0.0027158	0.0089843
75	0.0282548	0.0402030	0.0176446			0.0078044	0.0210944
Hispanic men							
45	0.0026056		0.0008874			0.0003907	0.0018822
55	0.0060763		0.0023285			0.0010255	0.0044408
65	0.0124837		0.0061026			0.0026905	0.0104592
75	0.0272090		0.0174811			0.0077317	0.0245326
Hispanic women							
45	0.0014800		0.0005763			0.0002537	0.0011839
55	0.0033205		0.0015124			0.0006659	0.0027946
65	0.0074147		0.0039665			0.0017476	0.0065894
75	0.0188635		0.0113849			0.0050268	0.0154967

Figure S1. Prevalence estimates of PAD according to odds of PAD at a given demographic variables in NHANES and meta-analyzed odds ratio for age, sex, and race/ethnicity from six cohorts.
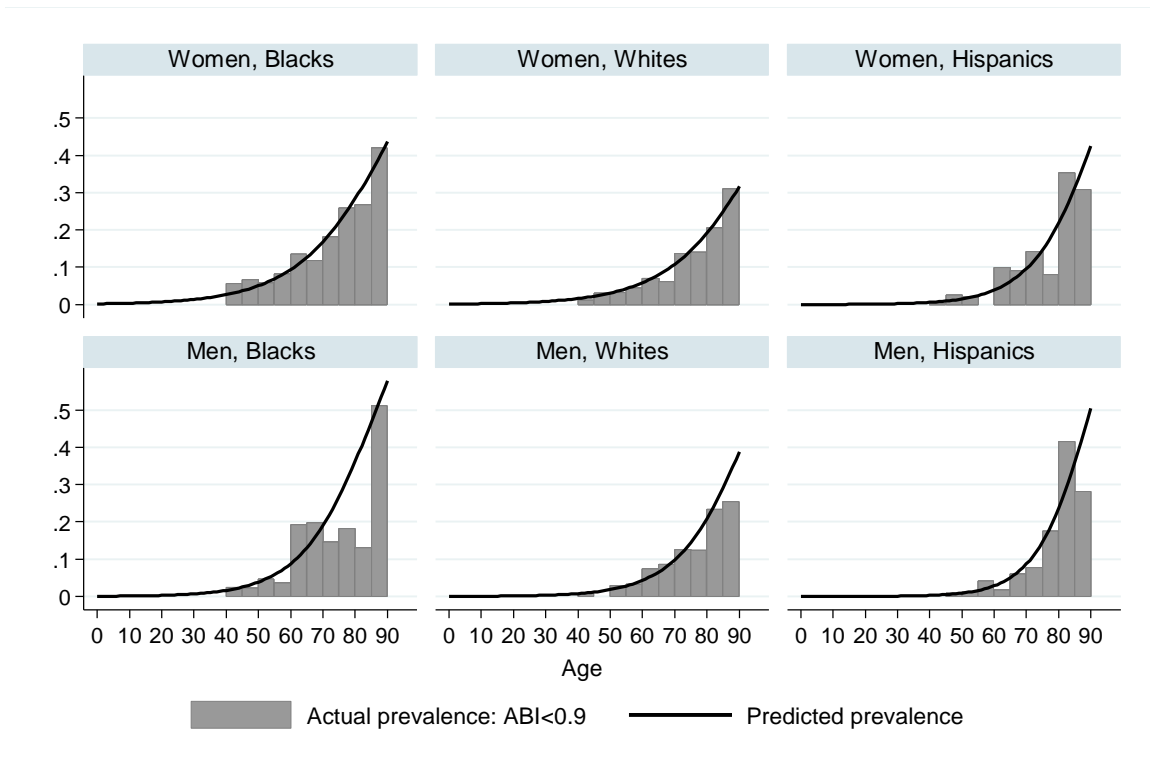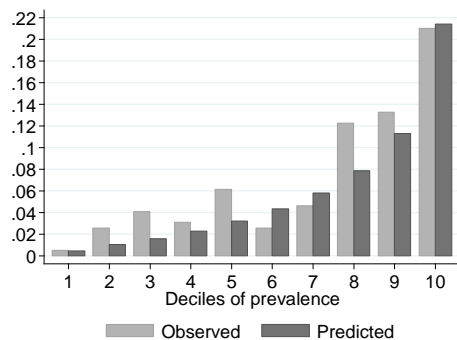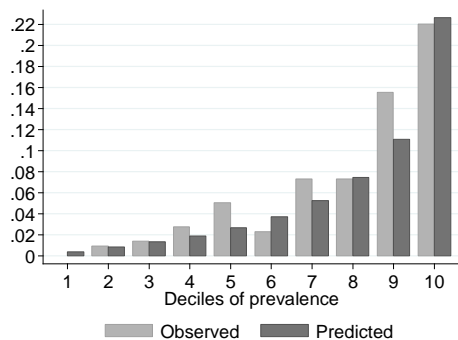
Figure S2. Observed vs. predicted risk of PAD by deciles of predicted risk (cross-validation by splitting NHANES according to 2-year cycles).
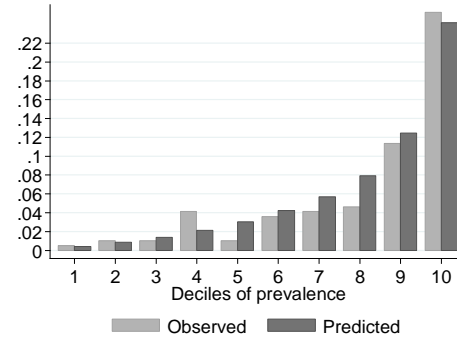
1. 1999-2002 for development and 2003-2004 for validation

2. 1999-2000 and 2003-2004 for development and 2001-2002 for validation

3. 2001-2004 for development and 1999-2000 for validation

		Statistics in a validation dataset			
		Chi² , p-value			C-statistic
Development	Validation	All deciles	Bottom 5 deciles	Top 5 deciles	
1999-2002	2003-2004	26.5, 0.0002	18.6, 0.0002	8.0, 0.14	0.736
1999-2000 & 2003-2004	2001-2002	14.1, 0.11	6.5, 0.27	7.7, 0.17	0.786
2001-2004	1999-2000	11.1, 0.28	6.7, 0.25	4.3, 0.54	0.801

Figure S3. Observed vs. predicted risk of PAD by deciles of predicted risk (NHANES 1999-2004).
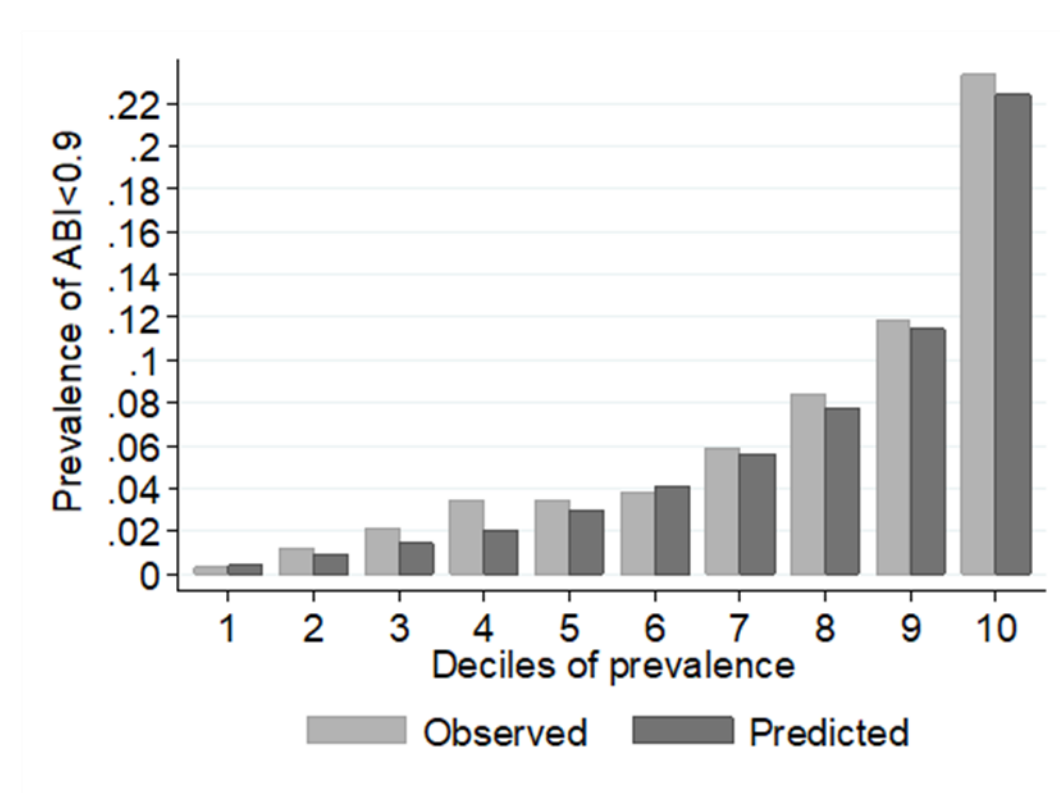
Chi^2 was 10.2 (p=0.35) in all deciles, 9.2 (p=0.08) in bottom 5 deciles, and 1.0 (p=0.95) in top 5 deciles. C-statistic was 0.77.

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