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Genetic ancestry and lower extremity peripheral artery disease in the Multi-Ethnic Study of Atherosclerosis

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Abstract

Using self-report of race/ethnicity, African Americans consistently have a higher prevalence of peripheral artery disease (PAD) compared to other ethnic groups. We aimed to determine the associations between estimated genetic admixture and PAD among African and Hispanic Americans. We studied the association between genetic ancestry and PAD among 1417 African and Hispanic American participants in the Multi-Ethnic Study of Atherosclerosis who were genotyped for ancestry informative markers (AIMs). PAD was defined as an ankle–brachial index (ABI) < 0.90. The overall prevalence of PAD among the 712 self-identified African American subjects was 15.2% and 4.6% among the 705 self-identified Hispanic Americans. A one standard deviation increment in European ancestry was associated with non-significant reductions in the odds for PAD among African (OR: 0.96 [95% CI: 0.78–1.18]) and Hispanic Americans (0.84 [0.58–1.23]), while the same increment in Native American ancestry was significantly associated with a lower odds of PAD in Hispanic Americans (0.56 [0.36–0.96]). Adjustment for demographic variables, field center, cardiovascular disease (CVD) risk factors and inflammatory markers strengthened the odds for European ancestry among African (0.85 [0.66–1.10]) and Hispanic Americans (0.68 [0.41–1.11]). The magnitude of the association for Native American ancestry among Hispanic Americans did not materially change (0.56 [0.29–1.09]). In conclusion, a higher percent Native American ancestry in Hispanics is associated with a lower odds of PAD while in both Hispanics and African Americans, greater European ancestry does not appear to be associated with lower odds for PAD.

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Keywords

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Introduction

Using the ankle-brachial index (ABI), previous studies have determined that 6 to 8 million Americans have peripheral artery disease (PAD)^{1–3} and that the prevalence of PAD differs by ethnic group. Specifically, African Americans have the highest prevalence of PAD, followed by Native Americans, Caucasian Americans, Hispanic Americans and Chinese Americans, although the differences between the latter three groups are relatively small. These racial/ethnic-specific differences in PAD persist after adjustment for cardiovascular disease risk factors.^{4,5} It is unclear whether genetic, social or environmental factors, or a combination thereof contribute to these differences.

Owing to its ease of use and reasonable estimation of individual ethnicity, self-reported ethnicity (SRE) is commonly used in epidemiologic/population-based research. Indeed, SRE is the standard for assessing ethnic diversity in the United States census. Prior studies on ethnicity and PAD have used SRE, which ignores the fact that African and Hispanic American groups in the US are admixed. That is, African Americans are often a combination of African and European ancestry, while Hispanic Americans may be of African, European and Native American ancestral backgrounds. Use of SRE also limits our ability to differentiate genetic or environmental factors associated with PAD because there is significant heterogeneity in the individual admixture among these ethnic groups.^{6,7} Hence, if genetic factors are responsible for higher PAD in these groups, the risk of PAD may vary by the amount of ancestral background of an individual, even within the same SRE category.

Genetic admixture analysis determines the different levels of ancestry for a given individual and how these may be related to the presence of specific phenotypes such as PAD. To do so, genetic markers called ancestry informative markers (AIMs) are ‘grouped’ into clusters along both continental lines and common self-identified racial groups (such as Native American, African).⁸ Ancestry informative markers have large frequency differences between different racial groups of common ancestry.^{6,7,9–11} Since African and Hispanic Americans are typically heterogeneous mixtures of ancestral populations, use of genetic admixture analysis provides increased sensitivity for potentially subtle differences in ancestry that may not be apparent when SRE is used and which may be relevant to the associations in question. Conversely, even when there is a significant association between ancestry and a given phenotype, the association may be confounded by environmental factors.¹² Adjustment for these factors could help clarify the strength and significance of the association between admixture and the phenotype. Therefore, using data from the Multi-Ethnic Study of Atherosclerosis (MESA), the aim of this study was to determine the association between PAD and estimated genetic ancestry.

Methods

Participants

Details about the aims and study design of the MESA have been published previously.¹³ In brief, between July 2000 and August 2002, 6814 men and women between the ages of 45 and 84 years and who self-identified themselves as African, Chinese, Hispanic, or non-Hispanic White American were recruited and participated in the baseline examination. Individuals with a history of physician-diagnosed or invasive procedure for cardiovascular disease were excluded. The institutional review boards at all participating centers approved the study and all participants gave informed written consent.

There were 6814 participants recruited into the MESA. Of these, 2847 were randomly selected within ethnic strata and then genotyped for AIMs. Seven hundred and 12 were African American, 705 were Hispanic American, 718 were Chinese American and 712 were Caucasian American. Since there is no significant admixture in Chinese Americans, and Caucasian American ancestry is used to characterize admixture in the African and Hispanic American participants, the final analytic sample for this analysis includes 1417 participants (712 African Americans and 705 Hispanic Americans).

Data collection

Standardized questionnaires were used to obtain demographic information and level of education, annual household income, smoking history, and medication usage for high blood pressure, high cholesterol, or diabetes. Cigarette smoking was defined as current, former, or never. Height and weight were measured with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Resting blood pressure was measured three times in seated participants with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon). Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or current use of an antihypertensive medication.

Laboratory

Blood was collected after a 12-hour fast and stored at -70°C . Dyslipidemia was defined as a total-cholesterol/ HDL-cholesterol ratio > 5.0 or use of cholesterol reducing medication. Diabetes was defined as fasting glucose ≥ 126 mg/dl or use of hypoglycemic medication. The estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) study formula.¹⁴

In addition to the indices listed above, measurements of the following classes of non-lipid biomarkers were conducted at either at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT) or the Biochemical Genetics Clinical Laboratory at Fairview-University Medical Center (Minneapolis, MN): inflammation (high-sensitivity plasma C-reactive protein, fibrinogen, interleukin-6), insulin concentration (fasting insulin) and hemostasis/fibrinolysis (factor VIII coagulant activity, plasmin-antiplasmin complex, D-dimer) as well as homocysteine.

Ancestry informative markers

Ancestry informative markers (AIMs) were genotyped in two separate panels and were chosen to maximize allele frequency differences among race/ethnic groups. In Panel 1, 97 single nucleotide polymorphisms (SNPs) were selected from an Illumina proprietary SNP database to maximize the difference in allele frequencies between Caucasians and African Americans, Caucasians and Chinese, or African American and Chinese. One SNP failed Illumina QC, resulting in 96 AIMs. In Panel 2, an additional 112 AIMs were selected from published lists that were informative for Hispanic ancestry.^{15,16} Six of these SNPs failed Illumina QC and an additional three SNPs were eliminated for technical reasons, resulting in 103 AIMs. Ancestral population genotype data was obtained from HapMap (60 Yoruban Nigerians) and previous genotype data collected on 345 participants from Native American populations.^{15,16} For the Caucasian pseudo-ancestral group, genotype data were used from the 712 MESA Caucasians. Illumina Genotyping Services (Illumina Inc., San Diego, CA, USA) performed genotyping using the GoldenGate assay. Characterization of population structure and estimation of genetic admixture was conducted as previously described by Wassel et al.¹⁷

Peripheral artery disease ascertainment

At the baseline MESA examination and at visit 3 (approximately 3 years later), systolic blood pressure measurements in the arms and legs were obtained using a hand-held Doppler instrument with a 5-mHz probe (Nicolet Vascular, Golden, CO, USA). Systolic blood pressures were measured in the bilateral brachial, dorsalis pedis, and posterior tibial arteries. To provide the highest sensitivity while maintaining roughly equivalent overall accuracy compared to other methods of calculating the ABI, the ABI was calculated using the lower of the systolic blood pressures in the dorsalis pedis or posterior tibial arteries and the higher of pressures in the two brachial arteries. The highest brachial artery pressure (right versus left) was used for the denominator to account for the possible influence of subclavian stenosis.¹⁸ The lower of the right versus left ABI was defined as the ABI for that participant. Peripheral artery disease was defined as an ABI < 0.90. Since an ABI < 1.00 has been shown to be significantly associated with higher levels of cardiovascular disease (CVD) risk factors, as well as subclinical atherosclerosis and incident CVD, we used this ABI cut-point in secondary analyses as a more liberal PAD definition.^{19–21} Individuals with an ABI > 1.40 were excluded from the analysis.

Statistical analysis

Baseline characteristics were compared across racial/ethnic groups and across tertiles of ancestry within racial/ethnic groups using *t*-tests, ANOVA, chi-square, Wilcoxon, or Kruskal–Wallis tests as appropriate. Logistic regression was used for prevalent PAD, as well as in sensitivity analyses where all (prevalent + incident) PAD outcomes were utilized. Ancestry was modeled as a continuous variable per standard deviation. We used the computer software ‘STRUCTURE’ to determine the number of ancestral populations necessary to analyze per ethnic group. For African Americans, this was determined to be two populations: European and African. Percent European ancestry + African ancestry = 100%, and thus only one of these two ($K-1 = 2-1 = 1$) is needed in a model to characterize

individual ancestry. Similarly, among Hispanics, it was determined that three ancestral populations was appropriate, and percent European ancestry + percent African ancestry + percent Native American ancestry = 100%. Thus, only two of three ancestry estimates ($K-1 = 3-1 = 2$) are needed to characterize individual ancestry among Hispanics. Staged models were used to examine potential confounders and assess the strength of traditional PAD risk factors as compared to individual percent ancestry. For analyses on Hispanic Americans, the models contained variables for European and Native American ancestry simultaneously. Potential confounders were chosen based on many previous studies of race/ethnicity and PAD.^{4,5}

Results

The characteristics of the African and Hispanic American participants are shown in Table 1. For both ethnic groups, the mean age was 61 years and roughly 55% were women. Compared to Hispanic Americans, African Americans had significantly higher levels of cigarette smoking, hypertension, BMI, D-dimer and homocysteine. Conversely, Hispanic Americans had significantly higher levels of dyslipidemia. Among African Americans the average percent European ancestry was 20.2% (SD: 15.9). For Hispanic Americans, the average percent European, African and Native American ancestry was 38.7% (21.9), 12.9% (18.9) and 48.3% (23.7), respectively.

The overall prevalence of an ABI < 0.90 among the 712 African American subjects was 15.2% while the prevalence among the 705 Hispanic Americans was 4.6%. These prevalence rates were similar to those not genotyped in the MESA cohort (16.0 and 5.9%, respectively). The characteristics of African and Hispanic Americans by prevalent PAD status are provided in Table 2. In both ethnic groups, those with PAD were significantly older and had significantly higher levels of hypertension, fibrinogen, D-dimer and homocysteine while having significantly lower levels of estimated glomerular filtration rate. Interleukin-6 was significantly higher in African Americans but not among Hispanic Americans. African Americans with PAD also had lower BMI, waist circumference and education levels. In both ethnic groups, European ancestry was not significantly different among those with and without PAD. In contrast, Native American ancestry was significantly lower among Hispanic Americans with PAD (34.6 vs 49.1%, $p = 0.01$).

The characteristics of the African American participants by tertile of European ancestry are provided in Table 3a. In African Americans, increasing European ancestry was associated with higher age, educational attainment and gross annual income but lower levels of hypertension, diastolic blood pressure, BMI and fibrinogen.

Among African Americans, a 1-SD increment in European ancestry was associated with a non-significant reduction in the odds for PAD (Figure 1). The odds ratios for this association ranged from 0.96 (95% CI: 0.78–1.18) in unadjusted models to 0.85 (0.66–1.10) with adjustment for demographic variables, field center, CVD risk factors and inflammatory markers.

Table 3b provides the characteristics of the Hispanic American participants by tertile of both European and Native American ancestry. In Hispanic Americans, increasing European ancestry was significantly associated with higher age, family history of coronary heart disease (CHD), LDL cholesterol and homocysteine but a significantly lower BMI. Native American ancestry among Hispanic Americans was significantly associated with lower age, HDL cholesterol, homocysteine and anti-hypertensive medication but significantly higher levels of diabetes, eGFR, BMI, waist circumference, C-reactive protein and interleukin-6. Among Hispanic Americans, there was a non-significant reduction in the odds for PAD with increasing increments of European ancestry (unadjusted: OR: 0.84 [95% CI: 0.58–1.23], fully adjusted: 0.68 [0.41–1.11]). Findings were stronger for the association between Native American ancestry and PAD among Hispanic Americans. That is, the unadjusted odds for PAD from a 1-SD increment in Native American ancestry was 0.56 [0.36–0.96]. With adjustment for demographic and CVD risk factors, the association remained statistically significant (0.46, $p < 0.01$; 0.53, $p = 0.05$; respectively). With additional adjustment for inflammatory factors, the magnitude of the point estimate for this association remained large and was unchanged but the association lost statistical significance (OR = 0.56, $p = 0.09$).

In sensitivity analyses, we evaluated whether the associations for European and Native American ancestry differed by changing the ABI cut-point to 1.00, or with the addition of incident cases of an abnormal ABI or lower extremity revascularization. In all cases, the magnitudes of the associations were modestly attenuated; however, the pattern of change of the associations with increasing adjustment for covariates was similar to that provided in Figure 1. For example, when the outcome for PAD was defined as total (prevalent and incident) cases of an ABI < 1.00 plus incident cases of lower extremity revascularization, the odds ratios for a 1-SD increment in European ancestry among African Americans ranged from 1.02 [0.88–1.19, unadjusted] to 0.91 [0.76–1.08, fully adjusted]. Using this same outcome and among Hispanic Americans, the odds ratios ranged from 0.91 [0.74–1.12, unadjusted] to 0.72 [0.54–0.94, fully adjusted] for 1-SD increments of European ancestry while the odds ratios ranged from 0.85 [0.69–1.04, unadjusted] to 0.62 [0.44–0.87, fully adjusted] for 1-SD increments in Native American ancestry.

Discussion

In this study of community dwelling individuals from six centers across the United States, increasing levels of Native American ancestry among Hispanic Americans were associated with a significantly lower odds for prevalent PAD (ABI < 0.90) in unadjusted analysis, as well as in models containing demographic and traditional CVD risk factors. With additional adjustment for inflammatory factors, the association was of borderline significance ($p = 0.09$). Of note, the magnitude of the association was relatively large and the same for both the unadjusted and final models (0.56), indicating that the addition of the inflammatory covariates used additional degrees of freedom that resulted in reduced power and the change in the p -value. Moreover, when PAD was defined as an ABI < 1.00 , the association remained statistically significant after adjustment for all risk factors. In African and Hispanic Americans, the association between European ancestry and PAD was not significant. Taken together, we believe the results of this study suggest that there is significant genetic variation within SRE groups in regards to prevalence of PAD. Moreover,

the study suggests that genetic differences may, in part, account for some of the observed differences in the prevalence of PAD by self-reported race, demonstrated in prior studies.

Some authors argue that the use of SRE “is an inaccurate representation of the inferred genetic clusters.”²² Others argue that use of SRE may provide useful information on ethnic origins.²³ However, self-reported race/ethnicity assumes relative homogeneity within a single SRE group and limits our ability to understand genetic versus social and environmental factors associated with complex phenotypes. Previous studies have shown high correlation between genetic clustering and SRE²³ but the ability to generalize these results across all SRE groups may be problematic, especially when ethnic groups from various geographic locations in the United States are considered.²⁴ Additionally, previous work has shown a very high proportion of African Americans to be of mixed genetic ancestry.⁷ Therefore, the use of SRE is likely to be an imperfect classification system that will result in residual confounding due to population substructure within the SRE strata.

Data from the Strong Heart Study (SHS) show that Native Americans have a prevalence of PAD that is higher than either Hispanic Americans or non-Hispanic Whites but lower than in African Americans.¹ In this context, we were surprised to find a lower risk of PAD associated with Native American ancestry among Hispanic Americans. However, in a fully adjusted model, the two-sided *p*-value for Native American ancestry among Hispanics, by Monte Carlo permutation analysis with 5000 replications, was 0.0104. Thus, we have confidence in the validity of the results for this association. The mechanisms responsible are uncertain, but we hypothesize that differences in acculturation may be responsible. In this regard, prevalence figures from population studies are influenced by both genetic and sociocultural factors. Therefore, the prevalence rates of Native Americans in the SHS may include effects of acculturation (such as diet and exercise habits) to the predominant US culture. In a separate study of Hispanic American MESA participants, we found a direct and significant correlation between level of acculturation and carotid intimal medial thickness²⁵ (a marker of subclinical atherosclerosis) indicating that those Hispanic Americans who retained their native cultural habits had less carotid atherosclerotic disease. Although uncertain, similar effects may have led to the high prevalence of PAD in Native Americans in the SHS. For example, the very high levels of obesity and diabetes may be due to effects of acculturation of Native Americans to the prevailing cultural norms. Importantly, diabetes is a strong and independent risk factor for PAD⁴ and may be contributing to the higher PAD prevalence rates in Native Americans who, from a genetic ancestry perspective, may actually have a relatively lower risk for this disease.

Strengths of this study include its relatively large sample size, a geographically diverse population and the large AIM panel with which to estimate ancestry. The study also has limitations. First, in the case of African ancestry, results trended strongly towards an association with PAD, but failed to reach statistical significance. Whether this was due to chance or to limited statistical power is uncertain. Future studies with greater numbers of individuals with PAD are required to confirm or refute this finding. While the study included a large number of AIMs, there were not sufficient AIMs to perform admixture mapping in order to identify regions in the genome where causal genes may be located. Additionally, by focusing on subclinical CVD measures as outcomes, the distribution of

these measures in the different ethnic groups may be truncated because potential participants with overt (more severe) CVD were excluded. Finally, while the participants came from six centers across the US, there may be regional differences in admixture that were not captured by our sampling design.

In conclusion, among Hispanic Americans residing in the United States, an increasing percentage of Native American ancestry was associated with a lower odds for PAD. Conversely, increased European ancestry was not associated with PAD among African or Hispanic Americans. These results suggest that, among Hispanic Americans, the associations between SRE and PAD in epidemiologic studies may be confounded by the degree of genetic admixture in a given individual. Future studies should genotype larger numbers of ancestry informative markers. These data might be used to admixture map regions of the genome so that specific genes or regions of the genome associated with PAD risk may be identified. When available, such information may provide novel understandings of the pathogenesis of PAD, and/or may ultimately identify novel targets for prevention and intervention.

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Figure 1.

The association between prevalent peripheral artery disease and genetic ancestry among African and Hispanic Americans: the Multi-Ethnic Study of Atherosclerosis (2000–2002). Vertical bars = 95% confidence interval. Model 1: unadjusted; Model 2: adjusted for age, sex, education > high school, income < \$40 000, site; Model 3: additionally adjusted for diabetes, hypertension, dyslipidemia (total/HDL > 5.0 or lipid-lowering medicines), BMI, pack years of smoking, family history (parent, sibling) of coronary heart disease (CHD); Model 4: additionally adjusted for IL-6, CRP, fibrinogen, homocysteine, D-dimer.

Table 1

Characteristics of African and Hispanic Americans: the Multi-Ethnic Study of Atherosclerosis (2000–2002)

Characteristic	African American (<i>n</i> = 712)	Hispanic American (<i>n</i> = 705)	<i>p</i> -value ^a
Age, years	61.5 ± 9.9	61.2 ± 10.1	0.47
Sex, <i>n</i> (%)			
Male	321 (45.1)	324 (46.0)	0.74
Female	391 (54.9)	381 (54.0)	
Field center, <i>n</i> (%)			
Wake Forest	179 (25.1)	1 (0.14)	< 0.001
Columbia	153 (21.5)	244 (34.6)	
Johns Hopkins	215 (30.2)	0 (0)	
Minnesota	0 (0)	202 (28.7)	
Northwestern	104 (14.6)	0 (0)	
UC-Los Angeles	61 (8.6)	258 (36.6)	
Education > high school, <i>n</i> (%)	492 (69.1)	239 (33.9)	< 0.001
Income \$40,000/year, <i>n</i> (%)	328 (46.1)	172 (24.4)	< 0.001
Current smoker, <i>n</i> (%)	135 (19.0)	106 (15.0)	0.04
Smoking pack-years ^b	1.9 (17.0)	0 (8.3)	< 0.001
Hypertension, <i>n</i> (%)	398 (55.9)	295 (41.8)	< 0.001
Diabetes, <i>n</i> (%)	119 (16.7)	121 (17.2)	0.84
Family history of CHD, <i>n</i> (%)	276 (38.8)	280 (39.7)	0.71
Systolic BP, mmHg	129.6 ± 20.9	126.0 ± 21.8	0.002
Diastolic BP, mmHg	73.9 ± 9.8	71.3 ± 10.3	< 0.001
Fasting glucose, mg/dl	107.0 ± 33.2	110.4 ± 40.5	0.08
Dyslipidemia, <i>n</i> (%) ^c	218 (30.6)	284 (40.3)	< 0.001
HDL cholesterol, mg/dl	52.9 ± 15.4	47.5 ± 12.6	< 0.001
LDL cholesterol, mg/dl	116.3 ± 33.0	119.9 ± 32.4	0.04
Body mass index, kg/m ²	30.1 ± 5.8	29.5 ± 5.1	0.04
C-reactive protein, mg/l ^b	2.59 (4.54)	2.43 (3.69)	0.52
D-dimer, µg/ml ^b	0.25 (0.31)	0.23 (0.25)	0.02
Interleukin-6, pg/ml ^b	1.4 (1.3)	1.4 (1.2)	0.94
Fibrinogen, mg/dl ^b	353.0 (97.0)	356.0 (88.0)	0.48
Homocysteine, µmol/l ^b	9.0 (3.4)	8.5 (2.9)	0.001

CHD, coronary heart disease; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

^a *p*-value by *t*-test, chi-square test, or Wilcoxon test as appropriate.^b Median (interquartile range).^c Dyslipidemia defined as total cholesterol/HDL cholesterol > 5.0.

Cohort characteristics by self-reported ethnicity and peripheral artery disease status: the Multi-Ethnic Study of Atherosclerosis (2000–2002)

Table 2

Characteristic	African American			Hispanic American		
	No PAD ^a (n = 601)	Prev. PAD (n = 108)	p-value ^b	No PAD ^a (n = 669)	Prev. PAD (n = 32)	p-value ^b
Age, years	60.6 ± 9.7	66.5 ± 9.3	<0.001	60.7 ± 9.9	69.4 ± 10.0	<0.001
Male sex, n (%)	273 (45.4)	47 (43.5)	0.71	305 (45.6)	364 (54.4)	0.40
Education > high school, n (%)	429 (71.5)	63 (60.6)	0.03	228 (34.1)	11 (34.4)	0.97
Income \$40,000, n (%)	287 (50.4)	41 (45.1)	0.35	168 (26.0)	4 (12.5)	0.09
Current smoker, n (%)	116 (19.3)	18 (17.3)	0.63	99 (14.8)	7 (21.9)	0.31
Smoking pack-years ^c	1.7 (16.4)	3.0 (23.0)	0.20	0.0 (7.1)	0.10 (23.7)	0.12
Hypertension, n (%)	317 (52.8)	78 (72.2)	<0.001	271 (40.5)	21 (65.6)	0.005
Diabetes, n (%)	99 (16.5)	19 (17.6)	0.78	107 (16.0)	14 (43.8)	<0.001
Estimated GFR (ml/min/1.73 kg)	86.8 ± 19.4	82.5 ± 19.7	0.04	82.4 ± 18.0	70.7 ± 24.6	0.01
Family history of CHD, n (%)	231 (38.4)	44 (40.7)	0.65	266 (39.8)	12 (37.5)	0.80
Systolic BP, mmHg	128 ± 19.8	137 ± 25.2	0.002	125 ± 21.0	143 ± 30.7	<0.001
Diastolic BP, mmHg	74 ± 9.6	75 ± 10.5	0.52	71 ± 10.2	72 ± 12.9	0.81
Fasting glucose, mg/dl	99.8 ± 33.0	99.0 ± 27.7	0.81	102.4 ± 38.7	121.3 ± 55.4	0.07
HDL cholesterol, mg/dl	52.4 ± 15.1	55.1 ± 16.7	0.10	47.5 ± 12.4	49.2 ± 16.2	0.56
LDL cholesterol, mg/dl	116.3 ± 32.8	118.2 ± 33.5	0.58	118.9 ± 31.5	141.1 ± 43.9	0.009
Dyslipidemia, n (%)	183 (30.5)	34 (31.5)	0.83	260 (38.9)	22 (68.8)	0.001
Body mass index, kg/m ²	30.3 ± 5.8	28.9 ± 5.2	0.02	29.6 ± 5.1	28.1 ± 4.3	0.11
Waist circumference, cm	101.4 ± 14.5	98.3 ± 13.8	0.04	100.5 ± 12.8	100.0 ± 11.6	0.83
C-reactive protein, mg/l ^c	2.5 (4.5)	2.7 (4.9)	0.85	2.4 (3.7)	2.4 (3.1)	0.70
Fibrinogen, mg/dl ^c	351 (101.0)	373 (96.0)	0.05	354 (89.0)	385 (100.0)	0.008
D-dimer, µg/ml ^c	0.23 (0.29)	0.32 (0.41)	<0.001	0.20 (0.24)	0.36 (0.37)	0.005
Interleukin-6, pg/ml ^c	1.3 (1.2)	1.7 (1.5)	0.001	1.4 (1.2)	1.6 (1.3)	0.12
Homocysteine, µmol/l ^c	8.9 (3.2)	9.8 (3.7)	0.002	8.4 (2.8)	9.9 (3.4)	0.003
Lipid-lowering medication use, n (%)	98 (16.4)	23 (21.3)	0.21	91 (13.6)	12 (37.5)	<0.001
Anti-HTN medication use, n (%)	279 (46.6)	69 (63.9)	0.001	211 (31.5)	18 (56.3)	0.004

Characteristic	African American		Hispanic American	
	No PAD ^a (<i>n</i> = 601)	Prev. PAD (<i>n</i> = 108)	No PAD ^a (<i>n</i> = 669)	Prev. PAD (<i>n</i> = 32)
				<i>p</i> -value ^b
European ancestry, % ^c	15.8 (22.5)	16.5 (15.7)	36.4 (32.5)	40.6 (27.6)
Native American ancestry, % ^c	N/A	N/A	49.1 (39.8)	34.6 (25.9)

GFR, glomerular filtration rate; CHD, coronary heart disease; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HTN, hypertension; N/A, not applicable.

^aExcludes ABI > 1.4; prevalent PAD = ABI < 0.9.

^b *p*-values by Wilcoxon, *t*-test or chi-square as appropriate.

 c Median (interquartile range).

Table 3a

Characteristics of African American participants by tertile of European ancestry: the Multi-Ethnic Study of Atherosclerosis (2000–2002)

Baseline characteristic	Tertile 1 (9.8%) <i>n</i> = 236	Tertile 2 (9.9–24.2%) <i>n</i> = 241	Tertile 3 (24.3%) <i>n</i> = 235	<i>p</i> -value ^a
Age, years	60.1 ± 9.8	62.3 ± 9.7	62.1 ± 10.0	0.03
Male sex, <i>n</i> (%)	110 (46.6)	116 (48.1)	95 (40.4)	0.20
Education > high school, <i>n</i> (%)	149 (63.7)	161 (67.7)	182 (77.5)	0.01
Income \$40,000/year, <i>n</i> (%)	94 (39.8)	106 (44.0)	128 (54.5)	0.02
Current smoker, <i>n</i> (%)	42 (17.8)	50 (20.8)	43 (18.3)	0.65
Hypertension, <i>n</i> (%)	139 (58.9)	145 (60.2)	114 (48.5)	0.02
Diabetes, <i>n</i> (%)	51 (21.6)	42 (17.4)	45 (19.2)	0.52
Family history of CHD, <i>n</i> (%)	89 (37.7)	92 (38.2)	95 (40.4)	0.81
Estimated GFR	85.7 ± 20.0	86.1 ± 18.6	86.5 ± 19.9	0.92
Systolic BP, mmHg	130.8 ± 21.3	130.4 ± 21.7	127.4 ± 19.4	0.15
Diastolic BP, mmHg	75.4 ± 10.5	73.7 ± 9.2	72.7 ± 9.5	0.01
Fasting glucose, mg/dl	107.5 ± 32.9	106.1 ± 31.7	107.4 ± 35.1	0.88
HDL cholesterol, mg/dl	53.8 ± 15.6	52.8 ± 15.7	52.0 ± 15.0	0.46
LDL cholesterol, mg/dl	113.1 ± 32.5	117.8 ± 31.6	118.1 ± 35.0	0.18
Dyslipidemia, <i>n</i> (%)	61 (25.9)	80 (33.2)	77 (32.8)	0.15
Body mass index, kg/m ²	30.9 ± 5.9	29.9 ± 5.8	29.6 ± 5.5	0.05
Waist circumference, cm	101.7 ± 14.7	100.4 ± 14.4	100.9 ± 14.4	0.61
C-reactive protein, mg/l ^b	2.8 (3.8)	2.8 (5.2)	2.3 (3.7)	0.74
Fibrinogen, mg/dl ^b	362.0 (109.0)	356.0 (84.0)	345.5 (92.0)	0.04
D-dimer, µg/ml ^b	0.23 (0.29)	0.25 (0.34)	0.23 (0.29)	0.69
Interleukin-6, pg/ml ^b	1.3 (1.1)	1.5 (1.3)	1.4 (1.3)	0.16
Homocysteine, µmol/l ^b	8.9 (3.4)	9.0 (3.2)	9.2 (3.5)	0.28
Lipid-lowering medication use, <i>n</i> (%)	42 (17.9)	45 (18.8)	35 (14.9)	0.51
Anti-HTN medication use, <i>n</i> (%)	120 (51.1)	135 (56.3)	96 (40.9)	0.003

CHD, coronary heart disease; GFR, glomerular filtration rate; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HTN, hypertension.

^a *p*-value by ANOVA, chi-square or Kruskal–Wallis as appropriate.

^b Median (interquartile range).

Table 3b

Characteristics of Hispanic American participants by tertile of European and Native American ancestry: the Multi-Ethnic Study of Atherosclerosis (2000–2002)

Baseline characteristic	European ancestry			Native American ancestry			<i>p</i> -value ^a
	Tertile 1 (<i>n</i> = 233)	Tertile 2 (<i>n</i> = 238)	Tertile 3 (<i>n</i> = 233)	Tertile 1 (<i>n</i> = 233)	Tertile 2 (<i>n</i> = 235)	Tertile 3 (<i>n</i> = 236)	
Age, years	59.6 ± 9.7	60.8 ± 10.1	63.1 ± 10.4	61.9 ± 10.6	62.3 ± 10.0	59.3 ± 9.5	0.002
Male sex, <i>n</i> (%)	103 (44.2)	108 (45.4)	112 (48.1)	103 (44.2)	106 (45.1)	114 (48.3)	0.64
Education > high school, <i>n</i> (%)	50 (21.5)	47 (19.8)	56 (24.0)	59 (25.3)	41 (17.5)	53 (22.5)	0.11
Income \$40,000/year, <i>n</i> (%)	48 (20.6)	61 (25.6)	62 (26.6)	70 (30.0)	48 (20.4)	53 (22.5)	0.07
Current smoker, <i>n</i> (%)	41 (17.6)	37 (15.6)	28 (12.0)	36 (15.5)	32 (13.6)	38 (16.1)	0.74
Hypertension, <i>n</i> (%)	91 (39.1)	96 (40.3)	107 (45.9)	102 (43.8)	107 (45.5)	85 (36.0)	0.08
Diabetes, <i>n</i> (%)	50 (21.5)	48 (20.2)	38 (16.3)	33 (14.2)	55 (23.4)	48 (20.3)	0.04
Family history of CHD, <i>n</i> (%)	84 (36.1)	84 (35.3)	112 (47.9)	99 (42.3)	96 (40.9)	85 (36.0)	0.34
Estimated GFR	82.3 ± 20.3	83.5 ± 16.2	80.1 ± 18.7	78.7 ± 17.5	82.1 ± 17.7	85.0 ± 19.7	0.001
Systolic BP, mmHg	125.7 ± 22.5	125.9 ± 21.0	126.2 ± 22.0	124.9 ± 20.7	127.1 ± 22.4	125.8 ± 22.2	0.55
Diastolic BP, mmHg	71.4 ± 10.7	70.9 ± 10.1	71.4 ± 10.0	72.0 ± 9.4	79.9 ± 10.0	70.9 ± 10.5	0.43
Fasting glucose, mg/dl	114.8 ± 51.8	109.0 ± 32.1	107.6 ± 34.8	105.1 ± 28.6	114.0 ± 43.9	112.2 ± 46.3	0.04
HDL cholesterol, mg/dl	46.9 ± 12.4	47.3 ± 12.1	48.5 ± 13.3	49.0 ± 12.5	48.2 ± 13.4	45.5 ± 11.7	0.006
LDL cholesterol, mg/dl	116.8 ± 31.3	118.6 ± 32.6	124.4 ± 32.8	122.3 ± 33.3	120.1 ± 32.4	117.4 ± 31.4	0.27
Dyslipidemia, <i>n</i> (%)	90 (38.6)	94 (39.5)	100 (42.7)	97 (41.5)	88 (37.5)	99 (42.0)	0.55
Body mass index, kg/m ²	30.4 ± 5.3	29.4 ± 4.9	28.9 ± 4.8	28.9 ± 5.2	29.0 ± 4.5	30.7 ± 5.3	<0.001
Waist circumference, cm	101.3 ± 12.9	99.9 ± 12.6	100.0 ± 12.8	98.8 ± 13.0	100.1 ± 11.8	102.3 ± 13.3	0.01
C-reactive protein, mg/l ^b	2.7 (4.1)	2.2 (3.3)	2.4 (4.0)	2.1 (3.4)	2.5 (3.7)	2.7 (3.9)	0.04
Fibrinogen, mg/dl ^b	359.5 (104.0)	345.0 (81.0)	357.5 (88.0)	364.0 (86.0)	357.0 (88.0)	343.0 (98.0)	0.21
D-dimer, µg/ml ^b	0.23 (0.27)	0.23 (0.26)	0.20 (0.24)	0.20 (0.22)	0.23 (0.32)	0.20 (0.22)	0.66
Interleukin-6, pg/ml ^b	1.5 (1.4)	1.4 (1.1)	1.3 (1.1)	1.3 (1.1)	1.3 (1.2)	1.5 (1.4)	0.02
Homocysteine, µmol/l ^b	8.4 (3.0)	8.3 (2.6)	8.8 (3.3)	8.8 (3.0)	8.2 (3.2)	8.4 (2.8)	0.04
Lipid-lowering medication use, <i>n</i> (%)	33 (14.2)	32 (13.5)	38 (16.2)	41 (17.5)	33 (14.0)	29 (12.3)	0.26
Anti-HTN medication use, <i>n</i> (%)	69 (29.6)	73 (30.7)	89 (38.0)	93 (39.7)	78 (33.2)	60 (25.4)	0.004

CHD, coronary heart disease; GFR, glomerular filtration rate; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HTN, hypertension.

^a *p*-value by ANOVA, chi-square or Kruskal–Wallis as appropriate.

^b Median (interquartile range).