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Association of Race and Peripheral Artery Disease: The Atherosclerosis Risk in Communities (ARIC) Cohort

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Abstract

Background: To evaluate the association of self-reported race with peripheral artery disease (PAD) and modification of this association by paraoxonase gene (*PON1, PON2* and *PON3*) single nucleotide polymorphisms (SNPs).

Methods: This cross-sectional study included 11,992 Black or White participants from the Atherosclerosis Risk in Communities (ARIC) cohort with *PON* genotyping. Ankle brachial index (ABI) was measured at baseline (1987-1989); PAD was defined as ABI < 0.90. Data also included demographic, health and behavioral information. Logistic regression was used to evaluate the association between race and PAD after adjustment for age, gender, BMI, education, smoking, high cholesterol, hypertension and diabetes. The associations between *PON* SNPs and PAD were also assessed.

Results: Blacks comprised 24.6% of the ARIC cohort; overall, 4.0% of participants had PAD. After adjustment for age, gender and BMI, Blacks had 1.27 times greater odds of PAD than Whites (95% CI = 1.04, 1.57), but this association became non-significant after adjustment for smoking, education, cholesterol, hypertension and diabetes. None of the SNPs evaluated met significance after Bonferroni correction for multiple comparisons ($p < 0.001$).

Conclusion: No association between race and PAD was identified after adjusting for health and behavioral covariates, suggesting that modifiable risk factors are major determinants of PAD. Further studies are needed to confirm this observation.

Keywords

Ankle-brachial index, ARIC, Paraoxonase, PAD, Peripheral artery disease, SNP, Single nucleotide polymorphism

Introduction

It is estimated that 12-20% of persons older than 60 years of age, or 8.5 million people in the US have peripheral arterial disease (PAD) [1]. PAD is a predictor of future CVD events, is prevalent worldwide, and found equally in men and women [1]. PAD occurs most often in the lower extremities and is defined as > 50% arterial stenosis as indicated by an ankle-brachial index (ABI) value < 0.9 [2]. ABI is a low cost, office-based assessment that accurately diagnoses PAD [2]. Normal ABI values range from 0.9 to 1.4 [2,3].

Risk factors for PAD include older age, high cholesterol, hypertension, diabetes and smoking [1]. Prior studies of the association between race and PAD have been inconsistent [4-6] with some reporting higher rates of PAD in Blacks but others failing to find racial differences. For instance, in 2.343 participants from the San Diego Population study, Criqui, et al. found that Blacks had higher odds of PAD (OR = 2.30, $p < 0.024$) than Whites after adjusting for covariates [7]. In contrast, there were no significant differences between Blacks and Whites in odds of PAD diagnosis (OR = 1.89; 95% CI = 0.89, 3.99) in a cohort of 403 patients from Houston, TX [8].

Additionally, genetics may modify the association between race and PAD. The development of atherosclerotic vascular diseases such as PAD are caused by oxidative damage from lipids and lipoproteins; this

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process may be mitigated by paraoxonase (*PON*) antioxidant enzymes [9-11] by reducing oxidative damage to low-density lipoproteins [12]. A recent case control study reported that *PON*1 concentrations and activities were lower in 66 PAD patients as compared to 8 controls [13]. Another case control study of 37 older participants (mean age 69.9 ± 9 years) with PAD found that *PON1* genotype and *PON*1 activity had direct relations to brachial flow-mediated vasodilation ($p = 0.0004$) [12]. To our knowledge, no previous study has examined the possibility that *PON* genes moderate the association between race and PAD.

Objectives: The purpose of this study was to examine the association of Black and White race with peripheral artery disease, and to evaluate the effect of paraoxonase single nucleotide polymorphisms (SNPs) on this association using data from the Atherosclerosis Risk in Communities (ARIC) [14] Study cohort.

Methods

This study was approved by the University of California San Diego Human Research Protections Program (#160359X) and data was collected through authorized access from dbGaP. The ARIC [14] study collected data at four sites and was supported by the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health; each site obtained institutional review board approval and written informed consent from participants. All data analyses were performed using SAS® University Edition (SAS Institute, Cary, NC).

ARIC

The Atherosclerosis Risk in Communities (ARIC) Study [14] is a prospective cohort study conducted in 4 communities in the United States (Washington County, MD; Forsyth County, NC; Jackson, MS; and Minneapolis, MN) each enrolling approximately 4,000 participants selected by probability sampling. A total of 15,972 study participants aged 45-64 years were examined at baseline (1987-1989) and re-examined every three years during four follow-up visits, with the last follow-up occurring in 2013. Since 2012, participants have been contacted annually by telephone to assess health status. Enrolled participants were Black (27%) and White (73%) men and women. Objectives were to investigate the etiology and natural history of atherosclerosis and to examine the risk factors and progression of subclinical to clinical cardiovascular disease events including coronary heart disease, heart failure, stroke and atrial fibrillation. In addition, the ARIC study examined genetic and environmental risk factors leading to ventricular dysfunction and vascular stiffness.

Participants

This study was limited to the 11,992 ARIC participants (24.6% Black, 75.4% White) with ABI values < 1.4 for whom *PON* genotyping data was available (Figure 1).

Variables

Race: In the ARIC [14] study, race was dichotomized as self-identified Black or White.

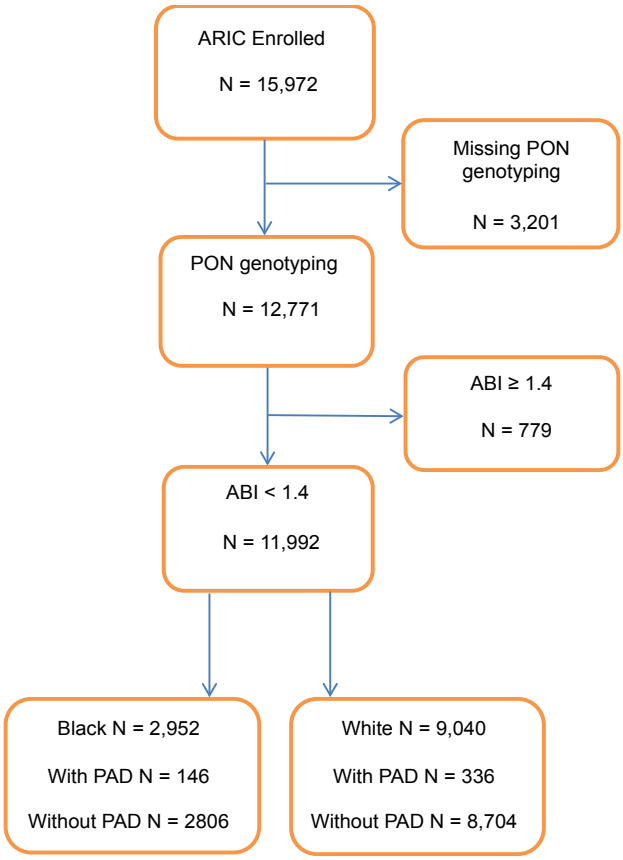

Figure 1: Sample population inclusion chart; ARIC, 1987-1989.

Peripheral artery disease: PAD was defined based on ABI values from the baseline visit. Single systolic blood pressure measures were taken in one upper extremity and one lower extremity to generate ABI values calculated as the ratio of lower to upper extremity [15]. Based on convention [1], participants with ABI values < 0.9 were categorized with PAD and participants with ABI values ≥ 0.9 and < 1.4 were categorized as normal and free of PAD. Participants with ABI values ≥ 1.4 (n = 779) were excluded from this analysis (Figure 1).

Covariates: Demographic characteristics (e.g., age, education, marital status), health history, body mass index (BMI) kg/m^2 and results of fasting laboratory assays were obtained from the baseline visit [14]. Family history included maternal and paternal CHD events. Current marital status (yes/no), high school graduate or more education (yes/no), current cigarette smoking (yes/no) and alcohol use (yes/no) were assessed at baseline. Measures of systolic and diastolic blood pressure were obtained and 12-hour fasting glucose and cholesterol levels were assayed from blood samples at baseline. Participants taking anti-diabetic medication or having fasting glucose ≥ 126 mg/dl were categorized as having diabetes mellitus [16]. Those taking cholesterol-lowering medication or having laboratory assessed cholesterol > 240 mmol/L were categorized as having high cholesterol [17]. Participants taking antihypertensive medications or having systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg were categorized as hypertensive [18]. Intake of current medications, including aspirin, anti-diabetic medication, antihypertensive medication and lipid lowering medication were determined by review of labelled containers [14] participants brought to the clinic visit.

Genotyping: Whole genome genotyping was performed using the Affymetrix 6.0 array platform [14]; there were 82 *PON* SNPs (43 *PON1*, 32 *PON2*, 7 *PON3*) available in the ARIC cohort which included (±) 20 kb window around each gene region. After excluding SNPs with minor allelic frequencies (MAF) < 5%, 62 SNPs remained available for screening analysis. All SNPs were in Hardy-Weinberg equilibrium and had ancestry-specific allele frequencies similar to those reported in publicly available databases (https://www.ncbi.nlm.nih.gov/projects/gapsolr/facets.html). The 62 SNPs were screened for significant association with PAD in Blacks and Whites combined and separately using a significance level of p < 0.001 (0.05/45) after Bonferroni correction for multiple comparisons confirmed 45 independent SNPs using the Nyholt method. Five principal com*PON*ent analysis covariates (PCs), obtained from the PLINK routine [19] were used to adjust for residual population stratification. SNPs were coded as continuous variables for analysis using an additive genetic model.

Statistical analysis: Descriptive statistics were calculated and reported as percentages for categorical variables and means (± standard deviations [SD]) for continuous data. Differences by race and PAD were analyzed using independent t-tests for continuous variables and chi-square analyses for categorical variables. All covariates were noncollinear based on correlation coefficients of r < 0.30. Covariates with at least marginally significant differences by race and presence of PAD as well as known confounders of the race-PAD association were retained for further analysis. Logistic regression was used to model the odds of PAD for Blacks compared to Whites. Statistical significance was defined as p < 0.05.

Forward stepwise multivariate logistic regression analysis was used to identify confounders (defined as a 10% change in the estimated coefficient between full and reduced models) and to assess the association between race and PAD, after adjustment for covariates. Model 1 examined the unadjusted association between race and PAD. Model 2 adjusted for age, gender and BMI. Model 3 adjusted for Model 2 variables and cigarette use. Model 4 adjusted for Model 3 variables and educational status. Model 5 adjusted for Model 4 variables and high cholesterol, hypertension and diabetes. None of the 62 *PON* SNPs screened met the significance criteria of p < 0.001) and were therefore not retained for further analysis. Interactions between race and covariates were evaluated with possible effect modification considered when p < 0.05.

Results

Table 1 shows baseline differences for Blacks and Whites in the ARIC cohort. Peripheral artery disease as defined by ABI < 0.90, was found in 482 (4.0%) participants, with a higher prevalence in Blacks (5.0%) than Whites (3.7%) (p = 0.003). Blacks were younger (53.3 ± 5.8 vs. 54.3 ± 5.7 years respectively, p < 0.0001), but had a higher mean BMI (29.6 ± 6.0 vs. 26.9 ± 4.8 kg/m^2, respectively, p < 0.0001) than Whites. There was a lower proportion of men (p < 0.0001) among Black participants and they were less likely to have a paternal (p < 0.0001) or maternal (p = 0.0002) family history of CVD than whites. Fewer Blacks used alcohol, completed a high school education, were married or used aspirin (p's < 0.0001). However, Blacks were more likely to smoke and to have a diagnosis of hypertension or diabetes (p's < 0.0001); there was no difference in prevalence of high cholesterol (p = 0.22).

Comparisons of baseline characteristics by PAD diagnosis showed that participants with PAD were significantly older (55.4 + 5.9 vs. 54.0 + 5.7 years, respectively (p = < 0.0001) and had a higher average BMI 28.1 ± 5.9 vs. 27.6 ± 5.2 kg/m^2 respectively, p = 0.018) (see Table 2). Those with PAD were more likely to be Black (p = 0.003), less likely to be male (p < 0.0001), and had a higher prevalence of smoking, hypertension, high cholesterol and diabetes (p's < 0.0001). However, those with PAD were less likely to be married (p = 0.0005), to

Table 1: Baseline characteristics by race; ARIC, 1987-1989 (n = 11992).

	Black (n = 2952)	**White (n = 9040)**	
	Mean (SD)	**Mean (SD)**	**p-value***
Age*	53.3 (5.8)	(54.3) (5.7)	< 0.0001
BMI (kg/m^2)	29.6 (6.0)	26.9 (4.8)	< 0.0001
	N (%)	N (%)	
Peripheral Artery Disease	146 (5.0)	336 (3.7)	0.0032
Male	1106 (37.5)	4212 (46.6)	< 0.0001
Family CVD History			
Paternal	531 (22.1)	2959 (35.4)	< 0.0001
Maternal	397 (15.0)	1558 (18.0)	0.0002
Marital Status	1745 (59.9)	7757 (87.1)	< 0.0001
High School Education	1766 (60.0)	7534 (83.4)	< 0.0001
Current Smoking Status	856 (29.0)	2229 (24.7)	< 0.0001
Current Alcohol Use	936 (32.0)	5907 (65.4)	< 0.0001
Hypertension	1625 (55.3)	2420 (26.9)	< 0.0001
High Cholesterol	753 (26.8)	2310 (25.6)	0.2231
Diabetes	565 (19.6)	776 (8.6)	< 0.0001
Aspirin	846 (29.1)	4735 (52.7)	< 0.0001

*Comparisons by race performed with t-tests for continuous variables and chi-square tests for categorical variables.

Table 2: Baseline characteristics by peripheral artery disease (PAD); ARIC, 1987-1989 (n = 11992).

	PAD† (n = 482)	**No PAD (n = 11510)**	
	Mean (SD)	**Mean (SD)**	**p-value***
Age (yr)	55.4 (5.9)	54.0 (5.7)	< 0.0001
BMI (kg/m^2)	28.1 (5.9)	27.6 (5.2)	0.0180
	N (%)	N (%)	
Black Race	146 (30.3)	2806 (24.4)	0.0032
Male	148 (30.7)	5170 (44.9)	< 0.0001
Family CVD History			
Paternal	142 (33.7)	3348 (32.3)	0.5482
Maternal	89 (19.9)	1866 (17.1)	0.1349
Marital Status	352 (74.1)	9150 (80.6)	0.0005
High School Education	338 (70.1)	8962 (78.0)	< 0.0001
Current Smoking Status	182 (37.8)	2903 (25.2)	< 0.0001
Current Alcohol Use	249 (52.0)	6594 (57.5)	0.0177
Hypertension	222 (46.3)	3823 (33.4)	< 0.0001
High Cholesterol	180 (37.9)	2883 (25.4)	< 0.0001
Diabetes	87 (18.2)	1254 (11.0)	< 0.0001
Aspirin	236 (49.3)	5345 (46.8)	0.2968

†PAD was defined as ABI values < 0.9;

*Comparisons performed with t-tests for continuous variables and chi-square tests for categorical variables.

have completed high school education (p < 0.0001) and to use alcohol (p = 0.018). None of the 62 *PON* SNPs in the ARIC population met the screening criterion for statistical significance (p < 0.001) and were therefore not retained for further analysis (Supplementary Table 1).

Step-wise logistic regression models (Table 3) showed that after adjusting for age, gender and BMI (Model 2), Blacks had 1.27 times greater odds of PAD than Whites (OR = 1.27, 95% CI = 1.04, 1.57). This association became non-significant in subsequent models that adjusted for cigarette use, educational status, high cholesterol, diabetes and hypertension (Models 3-5).

Main effects for all variables in Model 5 are shown in Table 4. Age, cigarette use, high cholesterol, hyperten-

Table 3: Association of race with peripheral artery disease (PAD) after adjustment for PAD risk factors and SNPs; results of multivariate logistic regression, ARIC, 1987-1989.

	N	OR (95% CI)	Variable(s) in model
Model 1	**11992**	**1.35 (1.11,1.65)***	**Race**
Model 2	11981	1.27 (1.04, 1.57)‡	Model 1 + Age, Gender, BMI
Model 3	11973	1.22 (0.99,1.50)	Model 2 + Cigarette use
Model 4	11962	1.17 (0.94,1.45)	Model 3 + Educational status
Model 5	11729	1.04 (0.83,1.30)	Model 4 + High cholesterol, Diabetes, Hypertension

Reference is White race; *p < 0.001; ‡p < 0.05.

Table 4: Adjusted independent associations of race, each covariate with PAD; results from multivariate logistic regression Model 5, ARIC, 1987-1989 (n = 11729).

	OR (95% CI)
Black Race	1.04 (0.83,1.30)
Age (per 1 yr)	1.04 (1.02,1.06)*
Gender (male)	0.54 (0.45 0.67)*
BMI (kg/m^2)	1.01 (0.99,1.03)
Cigarette Use (yes)	2.00 (1.64,2.44)*
Educational Status (yes)	0.86 (0.70,1.07)
High Cholesterol (yes)	1.53 (1.26,1.86)*
Diabetes (yes)	1.44 (1.11,1.87)†
Hypertension (yes)	1.43 (1.16,1.75)*

Reference is White race; Model adjusted for race, Age, Gender, BMI, Cigarette use, Educational status, High cholesterol, Diabetes and Hypertension; *p < 0.001, †p < 0.01.

sion (p's < 0.001) and diabetes (p < 0.01) were all significantly and independently associated with higher odds of PAD. Male gender was significantly associated with lower odds of PAD (p < 0.001). There were no significant interactions between race and any of the covariates.

Discussion

Atherosclerosis is the formation of fatty deposits of mostly low-density lipoprotein (LDL) cholesterol on the interior lining of the arterial walls [15]. Atherosclerosis manifests in a variety of ways, including peripheral artery disease (PAD) [4], and accounts for 1 in every 4 US deaths [20]. In this cross-sectional study of 11.992 ARIC cohort study participants, Blacks had higher odds of PAD (OR = 1.27, 95% CI = 1.04, 1.57) than Whites after adjustment for age, BMI, and gender, but this association was attenuated to non-significance after adjustment for comorbidities (i.e. hypertension and diabetes) and lifestyle risk factors (i.e. smoking, education). While this study did not find significant effect modification of *PON* SNPs on the association between race and PAD, to our knowledge this is the first study to report results of such an evaluation.

In this study of men and women aged 45 years and older from the ARIC cohort, there was a higher prevalence of PAD in Blacks than Whites (5.0% vs. 3.7%). These results are consistent with other [5,7], including Selvin, et al. who reported higher rates of PAD among Blacks than Whites (7.9% vs. 4.4%) using NHANES data [21]. Also, in accord with the NHANES data [21], we found a higher prevalence of cardiovascular disease risk factors including older age, higher BMI, current smoking, hypertension, high cholesterol and diabetes, among ARIC participants with PAD. However, our results suggested that race was not independently associated with PAD as adjustment for PAD risk factors such as smoking, hypertension and diabetes attenuated the association to non-significance. Results of the present study are in accord with Collins, et al., who also reported no association between race (Black or White) and PAD after adjustment for diabetes, smoking, hypertension and age [8].

In contrast, studies from selected populations have reported associations between race and PAD [5,7]. For example, the San Diego Population study [7] reported that Blacks had higher odds of PAD than Whites (OR = 2.30, p < 0.024). However, that study included participants with prior revascularization, which normalizes ABI, resulting in a higher prevalence of PAD than observed in ARIC. In addition, a study based on the MESA cohort reported that Blacks had significantly greater odds of PAD than Whites (OR = 1.67; 95% CI = 1.23, 2.26) after adjusting for multiple covariates [5]; however, MESA excluded those with known CVD, making a direct comparison with the ARIC cohort, which had no such exclusions, difficult.

The lack of a significant association between race and PAD after adjustment for health and behavioral CVD risk factors in the present study suggests that differences in PAD are influenced more by racial disparities in risk factors and their management rather than racial differences in the biological development of atherosclerosis. Prior research reports that Blacks present at a later clinical stage in the development of PAD than Whites. Furthermore, diabetes and neuropathy, both more prevalent in Blacks, affect the distal arteries and contribute to a PAD diagnosis [22]. Finally, it has been previously demonstrated that racial disparities exist in health care, with Blacks receiving lower quality than the majority of Whites in the United States [23-27].

The influence of genetic differences on the risk of

PAD is relatively unknown. *PON*1 enzymes have anti-inflammatory and antioxidant properties and may protect against atherosclerosis [28]. The enzyme is expressed in the liver and delivered to multiple tissues not expressing the enzyme [28]. Decreased *PON*1 enzyme activity has been shown to increase inflammation in animal studies, and increase oxidative stress among patients with atherosclerosis, diabetes and/or hypercholesterolemia [28]. Recent studies report associations between *PON* SNPs and atherosclerotic disease or related phenotypes. The *PON1* rs2299260 SNP was significantly associated with a 50% increased risk of resistant hypertension in European-Americans for each additional copy of the C allele [29]. Additionally, another *PON1* promoter region SNP, rs705379, was associated with blood pressure in middle-aged individuals [30]. However, others have failed to find an association between *PON1* polymorphisms and cardiovascular disease. In two separate meta-analyses, no association was found between a L55M *PON1* polymorphism and ischemic stroke [31], and no association was found between the 55L allele and stroke after adjusting for risk factors [32].

It is biologically plausible that there is an association between race and PAD after adjustment for risk factors. Previous studies show that Blacks have a thicker and stiffer aorta compared to Whites [33] and aortic stiffening may artificially lower ABI measures. Aboyans, et al. found that among the healthy participants of the MESA cohort, Blacks had ABI values approximately 0.2 lower than Whites [22]. We may have failed to find this association in adjusted models because of the small sample of Blacks relative to Whites in this cohort. Future studies assessing the genetic differences and gene-environment interactions with respect to PAD need to be evaluated across diverse ethnic study populations with adequate sample sizes [34].

Limitations

Several limitations and strengths of this study were considered. ABI may be underestimated due to categorization based on a single measure of systolic blood pressure from one upper and one lower extremity and rather than multiple measures in all extremities. The ARIC cohort may not be comparable to other cohorts such as MESA that have reported an association with race and PAD because of differences in selection criteria [35]. Misclassification due to self-identified race and ascertainment of other risk factors may contribute residual confounding affecting the estimation of the association between race and PAD. Here PAD was defined as ABI < 0.90 without consideration of prior revascularization, which would normalize ABI, potentially underestimating the prevalence of PAD [36]. Finally, this study excluded participants with an ABI ≥ 1.4 because of arterial stiffening due to calcification; it is estimated that PAD prevalence affects approximately 1% of persons in this group [7], resulting in an underestimation of the prevalence of PAD. This study also has several strengths including the use of data from a relatively large cohort of both Black and White men and women who were enrolled using a standardized protocol. This study also adjusted for educational status, which could contribute to differences in diagnosis, access to care and treatment. Finally, the effects of genetics as well as the interaction between race and PAD risk factors were examined.

Conclusions

While this study found an overall higher prevalence of PAD among Black participants, race was not significantly associated with PAD after adjusting for health and behavioral risk factors PAD. This suggests the risk of PAD may be modified through medical management and lifestyle changes. To our knowledge, this is the first study assessing the effect of the *PON* gene cluster (*PON1, PON2* and *PON2*) on the association between race and peripheral artery disease. Additional studies are needed to further assess the impact of genetics on the association between race and peripheral artery disease.

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Statement of ethical approval

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Statement of conflict of interest

No conflicts of interest.

Declaration of contribution of authors

All authors who significantly contributed to this manuscript have been listed.

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References

1. (2018) Centers for Disease control and prevention. Peripheral arterial disease (PAD) Fact sheet.
2. Philip Greenland, Joseph S Alpert, George A Beller, Emelia J Benjamin, Matthew J Budoff, et al. (2010) ACCF/AHA Guideline for assessment of Cardiovascular risk in asymptomatic adults. J Am Coll Cardiol 56: e50-e103.
3. Allison MA, Cushman M, Solomon C, Aboyans V, McDermott MM, et al. (2009) Ethnicity and Risk factors for change in the ankle-brachial index: The Multi-ethnic study of atherosclerosis. J Vasc Surg 50: 1049-1056.
4. Allison MA, Ho E, Denenberg JO, Langer RD, Newman AB, et al. (2007) Ethnic-specific prevalence of peripheral arterial disease in the United States. Am J Prev Med 32: 328-333.
5. Allison MA, Criqui MH, McClelland RL, Scott JM, McDermott MM, et al. (2006) The Effect of novel cardiovascular risk factors on the ethnic-specific odds for peripheral arterial disease in the multi-ethnic study of atherosclerosis (MESA). J Am Coll Cardiol 48: 1190-1197.

6. Weatherly BD, Nelson JJ, Heiss G, Chambless LE, Sharrett AR, et al. (2007) The Association of the ankle-brachial index with incident coronary heart disease: The Atherosclerosis Risk in Communities (ARIC) study, 1987-2001. BMC Cardiovasc Disord 7.
7. Criqui MH, Vargas V, Denenberg JO, Ho E, Allison M, et al. (2005) Ethnicity and peripheral arterial disease: The San Diego population study. Circulation 112: 2703-2707.
8. Collins TC, Petersen NJ, Suarez-Almazor M, Ashton CM (2005) Ethnicity and Peripheral arterial disease. Mayo Clin Proc 8: 48-54.
9. Strzyzewski KW, Piorunska-Stolzmann M, Majewski W, Kasprzak M, Strzyzewski W (2013) Effect of surgical treatment on lipid peroxidation parameters and antioxidant status in the serum of patients with peripheral arterial disease. Dis Markers 35: 647-652.
10. Arslan C, Altan H, Bersirli K, Aydemir B, Kiziler AR, et al. (2010) The role of oxidative stress and antioxidant defenses in Buerger disease and atherosclerotic peripheral arterial occlusive disease. Ann Vasc Surg 24: 497-503.
11. Abello D, Sancho E, Camps J, Joven J (2014) Exploring the role of paraoxonases in the pathogenesis of coronary artery disease: A systematic review. Int J Mol Sci 15: 20997-21010.
12. Pasqualini L, Cortese C, Marchesi S, Donatella S, Pirro M, et al. (2005) Paraoxonase-1 activity modulates endothelial function in patients with peripheral arterial disease. Atherosclerosis 183: 349-354.
13. Hernandez-Aguilera A, Sepulveda J, Rodriguez-Gallego E, Guirro M, Garcia-Heredia A, et al. (2015) Immunohistochemical analysis of paraoxonases and Chemokines in Arteries of Patients with Peripheral Artery Disease. Int J Mol Sci 16: 11323-11338.
14. (2018) Atherosclerosis risk in communities study (ARIC).
15. Aviram M (1999) Does Paraoxonase play a role in susceptibility to cardiovascular disease? Molecular Medicine Today 5: 381-386.
16. (2006) World Health Organization/International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: Report of a WHO/IDF consultation. WHO Press, Geneva, Switzerland.
17. (2001) National Heart, Lung and Blood Institute. National Cholesterol Education Program: ATO III Guidelines At-A-Glance Quick Desk Reference.
18. World Health Organization, International Society of Hypertension Writing Group (2003) World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 21: 1983-1992.
19. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, et al. (2007) PLINK: A tool set for whole-genome association and population-based linkage analyses. AM J Hum Genet 81: 559-575.
20. Centers for Disease Control and Prevention (2018) Heart Disease Facts.
21. Selvin E, Erlinger TP (2004) Prevalence of and risk factors for peripheral arterial disease in the United States: Results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation 110: 738-743.
22. Aboyans V, Criqui MH, McClelland RL, Allison MA, McDermott MM, et al. (2007) Intrinsic contribution of gender and ethnicity to normal ankle-brachial index values: The Multi-Ethnic Study of Atherosclerosis (MESA). J Vasc Surg 45: 319-327.
23. Schneider EC, Zaslavsky AM, Epstein AM (2002) Racial disparities in the quality of care for enrollees in Medicare managed care. JAMA 287: 1288-1294.
24. Institute of Medicine (2002) Unequal treatment: Confronting racial and ethnic disparities in health care. National Academy Press, Washington.
25. Ayanian JZ, Weissman JS, Chasan-Taber S, Epstein AM (1999) Quality of care by race and gender for congestive heart failure and pneumonia. Med Care 37: 1260-1269.
26. Virnig BA, Lurie N, Huang Z, Musgrave D, McBean AM, et al. (2002) Racial variation in quality of care among Medicare+Choice enrollees. Health Aff (Millwood) 21: 224-230.
27. Kahn KL, Pearson ML, Harrison ER, Desmond KA, Rogers WH, et al. (1994) Health care for black and poor hospitalized Medicare patients. JAMA 271: 1169-1174.
28. Litvinov D, Mahini H, Garelnabi M (2012) Antioxidant and anti-inflammatory role of paraoxonase 1: Implication in arteriosclerosis disease. N Am J Med Sci 4: 523-532.
29. Fontana V, McDonough CW, Gong Y, Rouby NM, Sa ACC, et al. (2014) Large-scale Gene-centric analysis identifies polymorphisms for resistant hypertension. J Am Heart Assoc.
30. Aviram M, Davies KJA (2004) Introduction to the serial review on paraoxonases, oxidative stress and cardiovascular diseases. Free Radic Biol Med 37: 1301-1303.
31. Dahabreh IJ, Kitsios GD, Kent DM, Trikalinos TA (2010) Paraoxonase 1 polymorphisms and ischemic stroke risk: A systematic review and meta-analysis. Genet Med 12: 606-615.
32. Banerjee I (2010) Relationship between paraoxonase 1 (*PON*1) gene polymorphisms and susceptibility of stroke: A meta-analysis. Eur J Epidemiol 25: 449-458.
33. Ferreira AV, Viana MC, Mill JG, Asmar RG, Cunha RS (1999) Racial differences in aortic stiffness in normotensive and hypertensive adults. J Hypertens 17: 631-637.
34. Hazarika S, Annex BH (2017) Biomarkers and genetics in peripheral artery disease. Clin Chem 63: 236-244.
35. (2018) Multi-ethnic study of atherosclerosis (MESA).
36. Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, et al. (1985) The prevalence of peripheral arterial disease in a defined population. Circulation 71: 510-515.

Supplemental Table 1: Association of SNP with peripheral artery disease (PAD) by race; Screening results of univariate logistic regression, ARIC, 1987-1989.

	Black	White
	p-value	p-value
PON1 SNPs		
rs2057681	0.9947	0.8722
rs3917527	0.8375	0.5322
rs2301711	0.1360	0.6351
rs2299260	0.5123	0.1003
rs2299261	0.8122	0.2193
rs854568	0.2244	0.1633
rs13223537	0.1535	0.0684
rs705378	0.9282	0.4397
rs854569	0.5176	0.4767
rs17166829	0.0805	0.7485
rs3917538	0.4571	0.4571
rs3917521	0.5483	0.9439
rs854565	0.1548	0.0647
rs854566	0.3861	0.0875
rs2237583	0.0781	0.6137
rs854572	0.9750	0.1455
rs3917541	0.6250	0.4097
rs3917551	0.6899	0.5496
rs3917550	0.2443	0.9268
rs2074354	0.7320	0.7374
rs3917490	0.6549	0.8163
rs2299262	0.9118	0.4064
rs854571	0.6993	0.8011
rs13236941	0.9029	0.5255
rs2272365	0.9712	0.3879
rs705382	0.9449	0.2007
rs2269829	0.9903	0.8249
rs2299257	0.4264	0.3982
PON2 SNPs		
rs2299267	0.2237	0.6372
rs43037	0.4647	0.0695
rs7778623	0.8670	0.6447
rs43052	0.4381	0.1883
rs4729190	0.4182	0.3619
rs1557782	0.7779	0.7316
rs43063	0.1277	0.2860
rs6958904	0.3154	0.8105
0.8105	0.0753	0.6131
rs7785039	0.7217	0.2540
rs3757707	0.5383	0.2228
rs43061	0.0432‡	0.1082
rs43065	0.8161	0.8751
rs2374993	0.5561	0.3062
rs10241004	0.0527	0.0792
rs10261470	0.4254	0.3101
rs10953151	0.9777	0.2626
rs6973380	0.0277‡	0.5168
rs10487133	0.6886	0.0118‡
rs7493	0.0280‡	0.6093
rs12534203	0.6239	0.2769
rs10953149	0.7062	0.4616
rs12535571	0.8454	0.6763
rs1639	0.0244‡	0.4959
rs43044	0.9125	0.0821
rs6950550	0.1685	0.4825
rs12530498	0.4852	0.9222
rs43048	0.3622	0.0228‡
rs7802018	0.4710	0.8903
PON3 SNPs		
rs468	0.1868	0.0344‡
rs1053275	0.7866	0.2072
rs11768074	0.6982	0.1708
rs9641162	0.0793	0.9115
rs10953143	0.4628	0.2114

References: *p < 0.001; ‡p < 0.05.