Scientific Research Publishing

Advances in Aging Research, 2020, 9, 77-93
https://www.scirp.org/journal/aar
ISSN Online: 2169-0502
ISSN Print: 2169-0499

Association of Race and Change in Ankle-Brachial Index: The Atherosclerosis Risk in Communities (ARIC) Cohort

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How to cite this paper: Franey, E.G., Kritz-Silverstein, D., Richard, E.L., Alcaraz, J.E., Nievergelt, C.M., Shaffer, R.A. and Bhatnagar, V. (2020) Association of Race and Change in Ankle-Brachial Index: The Atherosclerosis Risk in Communities (ARIC) Cohort. *Advances in Aging Research*, **9**, 77-93.
https://doi.org/10.4236/aar.2020.95007

Received: September 5, 2020
Accepted: September 27, 2020
Published: September 30, 2020

Abstract

Objective: This study evaluates the association of self-reported race with change in ankle-brachial index (ABI) over time and modification of this association by paraoxonase gene (*PON*1, *PON*2 *and PON*3) single nucleotide polymorphisms (SNPs). **Methods:** This longitudinal study included 11,992 (N = 2952 Black, N = 9040 White) participants from the Atherosclerosis Risk in Communities (ARIC) cohort with PON genotyping. Mixed-effects models examined whether race was associated with change in ABI over time after adjustment for known peripheral artery disease (PAD) risk factors. **Results:** Change in ABI over time differed between Whites and Blacks (race-time interaction, $p < 0.0001$). Stratified analyses showed that ABI values were better in both Blacks and Whites who completed high school or more education compared to those who completed less education. None of the *PON* SNPs met the significance level ($p < 0.001$) after Bonferroni correction for multiple comparisons. **Conclusions:** ABI differences by race were small and although statistically significant, may not be clinically significant. Change in ABI over time varies by race and may be modified by education. Results suggest that higher education may influence the lifestyle and behavioral choices contributing to better ABI in both Blacks and Whites. Further studies are needed to confirm this observation.

Keywords

Ankle-Brachial Index, ARIC, Paraoxonase, PAD, Peripheral Artery Disease,

SNP, Single Nucleotide Polymorphism

1. Introduction

Peripheral artery disease (PAD) occurs most often in the lower extremities and is the third leading cause of atherosclerotic cardiovascular death after coronary artery disease and stroke [1]. Risk factors for PAD include older age, high cholesterol, hypertension, diabetes and smoking [2]. The ankle-brachial index (ABI) is a reproducible and valid measure for diagnosing PAD; and has been the primary screening tool for PAD during the past few decades [2] because it is a low cost, non-invasive, office-based test [3]. By convention, ABI < 0.9 indicates >50% arterial stenosis whereas normal ABI ranges from ≥0.90 to <1.40 [4] [5].

Previous studies report that ABI is a subclinical predictor of cardiovascular events [6] [7] [8] [9]. In 13,150 participants from the ARIC cohort, Gupta *et al.* found a 40% (95%CI = 1.12, 1.74) increased risk of heart failure in those with low ABI (<0.90) compared to those with normal ABI (1.01 - 1.40) [6]. Yeboah *et al.*, in 1330 participants from the MESA cohort, found that ABI was an independent predictor of incident CHD/CVD beyond traditional risk factors for individuals of intermediate risk [7]. A meta-analysis of 16 population studies found that both low (≤0.9) and high ABI (>1.4) were significant independent predictors of CVD events and recommended inclusion of ABI to enhance the Framingham Risk Score for CVD risk prediction [8]. In the ARIC cohort, each 0.10 decline in ABI was associated with greater increase CHD hazard in Blacks than Whites [9].

PAD is prevalent worldwide and found in all US ethnic groups [3]. Some, but not all, studies report that Blacks have a higher prevalence of PAD compared to Whites [2] [3] [10], independent of traditional cardiovascular risk factors [4] [11]. However, to our knowledge, the association between race and change in ABI over multiple time points has not been previously reported.

Genetics may modify the association between race and ABI. Oxidative damage to lipids and lipoproteins contributes to the development of atherosclerotic vascular diseases such as PAD. Previous studies report that this progression may be mitigated by paraoxonase (PON) antioxidant enzymes [12] [13] [14] through reduction in low-density lipoprotein oxidation [15]. For example, in a case study of 37 older people (mean age 69.9 ± 9 years) with PAD, *PON*1 genotype and PON1 activity were directly related to brachial flow-medicated vasodilation (p = 0.0004) [15]. Furthermore, among 66 PAD patients and 8 controls, PON1 concentrations and activities were decreased in individuals with PAD [16]. However, the potential modification of any race-ABI association by genetic factors has not been reported.

The purpose of this study was to evaluate the association of Black and White race with change in ankle-brachial index over time, and to evaluate the effect of

paraoxonase single nucleotide polymorphisms (SNPs) on this association using data from a large well-characterized sample of older men and women.

2. Materials and Methods

This study used data from the ARIC [17] cohort with genetic data collected through authorized access from dbGaP. The multi-site ARIC study was supported by the National Heart, Lung and Blood Institute of the National Institutes of Health; each site obtained institutional review board approval and written informed consent from study participants prior to participation. This study was approved by the University of California San Diego Human Research Protections Program (#160359X); all analyses were performed using SAS® University Edition (SAS Institute, Cary, NC).

The Atherosclerosis Risk in Communities Study (ARIC) [17]: is a prospective cohort study investigating the etiology of atherosclerosis, examining the risk factors and progression of subclinical to clinical cardiovascular disease events conducted in 4 communities in the United States (Washington County, MD; Forsyth County, NC; Jackson, MS; and Minneapolis, MN) with each enrolling approximately 4000 participants selected by probability sampling. Secondary study objectives examined environmental and genetic risk factors leading to vascular stiffness. A total of 15,972 study participants aged 45 - 64 years consisting of Black (27%) and White (73%) men and women were examined at baseline and re-examined during four follow-up visits through 2013. Data for this analysis was collected at baseline (1987-1989), visit 3 (1993-1995) and visit 4 (1996-1998).

Participants: There were 11,992 ARIC participants (24.6% Black; 75.4% White) with ABI values < 1.4 for whom *PON* genotyping data was available (**Figure 1**). Of these, the 7672 participants (5925 Whites; 1747 Blacks) who completed a baseline and at least one follow-up visit where ABI was measured, were included in the mixed effects repeated measures analysis.

Variables

Race: In the ARIC [17] study, race was categorized based on self-identification as Black or White.

Ankle-Brachial Index: Single systolic blood pressure measures were taken in one upper extremity and one lower extremity at baseline, visit 3 and visit 4 [17]; ABI values were calculated as the ratio of lower to upper extremity blood pressure [6] with ABI < 0.9 [23] considered diagnostic of PAD and participants with ABI ≥ 1.4 (n = 779) excluded from this analysis (**Figure 1**).

Covariates: Health history, demographic characteristics (e.g., age, education, marital status), body mass index (BMI) kg/m^2 and results of 12-hour fasting laboratory assays as well as measures of systolic and diastolic blood pressure were obtained at the baseline visit [17]. ARIC 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. Participants taking cholesterol-lowering medication or having cholesterol > 240 mmol/L were categorized as having high cholesterol [18]; those taking anti-diabetic medication or having fasting glucose ≥ 126 mg/dl were categorized as having diabetes mellitus [19] and those taking antihypertensive medications or having systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg were categorized as hypertensive [20]. Current medication use including aspirin, anti-diabetic and antihypertensive medication and lipid lowering medication was determined by review of labelled containers [17] brought by participants to the baseline clinic visit.

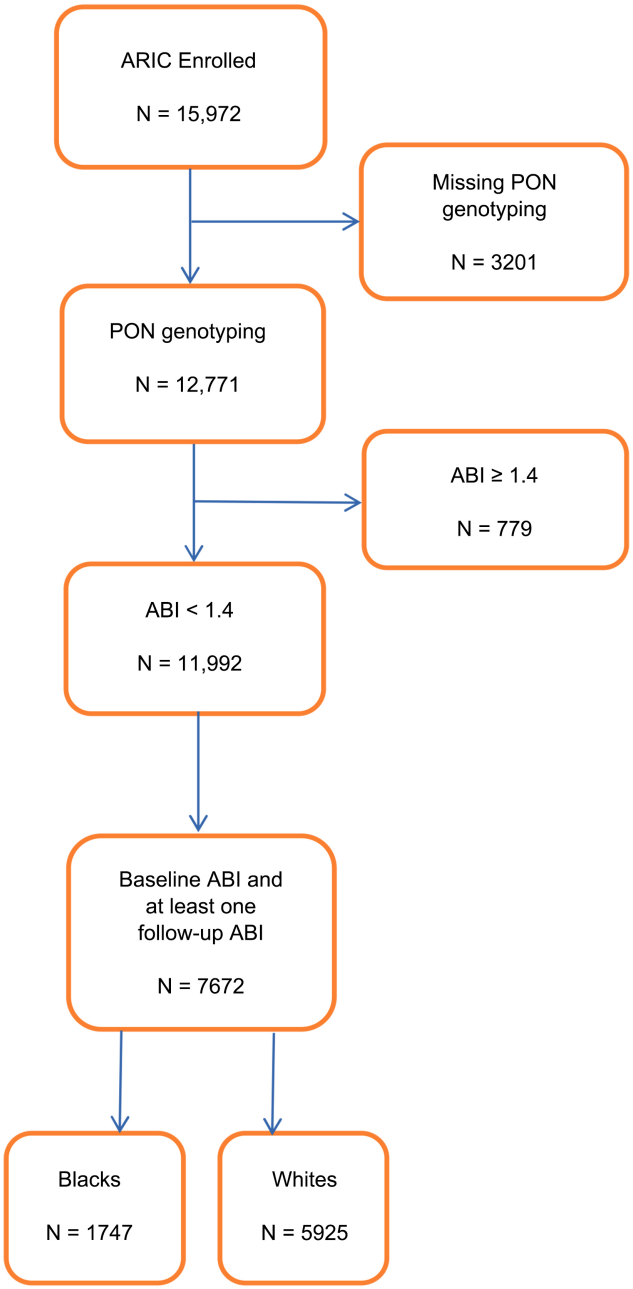


Figure 1. Flow chart sample derivation; ARIC, 1987-1989.

Genotyping: There were 82 *PON* SNPs (43 *PON*1, 32 *PON*2, 7 *PON*3) available in the ARIC cohort which included (±) 20 kb window around each gene region. Whole genome genotyping was performed using the Affymetrix 6.0 array platform [14]. SNPs with minor allelic frequencies (MAF) less than 5% were excluded from the analysis, leaving 62 SNPs 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 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 (https://neurogenetics.qimrberghofer.edu.au/matSpDlite/). Five principal component analysis covariates obtained from the PLINK routine [21] were used to adjust for residual population stratification.

Statistical Analysis: ABI values were analyzed as a continuous variable. Baseline descriptive statistics were calculated and reported as rates for categorical data and means (± standard deviations [SD]) for continuous data. Differences by race and baseline ABI were examined using independent t-tests for continuous variables and chi-square analysis for categorical variables. All covariates were noncollinear as determined by a correlation coefficient of ($r < 0.30$). Covariates as well as known confounders with at least marginally significant differences by race and baseline ABI were retained for further analysis. Mixed-effects models were used to assess the association between race and change in ABI over time as well as change in ABI over time within race. Results were reported as least squares (LS) means for participants with a baseline ABI and at least one follow-up (visit 3 or visit 4) ABI (mixed modelling adjusts for follow-up visit missing data). Statistical significance was defined as $p < 0.05$.

Covariates significantly associated with ABI ($p < 0.05$) in the repeated measures model were retained for multivariable analysis. Non-significant covariates were removed using a backward step-wise model selection removing the covariate with the largest p-value first and comparing full and reduced models. Where the likelihood ratio test was $p < 0.05$ and the covariates were $p < 0.05$, the covariate was retained in the final model. Interactions between race and covariates in the final model with $p < 0.05$ were considered potential effect modifiers and stratified in the final adjusted mixed-effects repeated measures model.

3. Results

Baseline differences between Blacks and Whites are shown in **Table 1**. Average baseline ABI was lower in Blacks than Whites (1.12 ± 0.13 vs. 1.13 ± 0.13, respectively; $p = 0.0003$). Compared to Whites, Black participants were younger (54.3 ± 5.7 vs. 53.3 ± 5.8 years respectively; $p < 0.0001$) and had higher mean BMI (26.9 ± 4.8 vs. 29.6 ± 6.0 kg/m^2, respectively; $p < 0.0001$). There was a lower proportion of men among Black participants ($p < 0.0001$) and they were less

Table 1. Baseline characteristics by race; ARIC, 1987-1989 (n = 11,992).

	Black (n = 2952)	White (n = 9040)	
	Mean (SD)	Mean (SD)	p-value*
Baseline ABI	1.115 (0.131)	1.125 (0.128)	0.0003
Age (yr)	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 (%)	
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

*Race differences: comparisons performed with t-tests for continuous variables, chi-square tests for categorical variables.

likely to have a paternal ($p < 0.0001$) or maternal ($p = 0.0002$) family history of CVD than White participants. Blacks were also less likely to use alcohol, to have completed high school education or more, to be married and to be taking aspirin (p's < 0.0001); Blacks were more likely to have hypertension, diabetes and be current smokers (p's < 0.0001), but there was no significant difference by race in prevalence of high cholesterol ($p = 0.22$) between Black and White participants. Of the 62 *PON* SNPs screened, none met the criterion for statistical significance ($p < 0.001$) and were therefore, not retained for further analysis (**Supplemental Table A**).

A mixed-effects model assessing the association between race and change in ABI over follow-up showed a significant race-time interaction (see **Table 2**). Additionally, among the covariates, adjusted analyses showed that older age ($p < 0.05$), as well as cigarette use, high cholesterol, diabetes and hypertension (p's < 0.0001) were each independently associated with lower ABI overall (worse), while male gender and a high school or more education were each independently associated with higher ABI overall (better) (all $p < 0.0001$).

Table 2. Association of race with change in ankle-brachial index; estimated coefficients from fixed effects; mixed-effect model repeated measures; ARIC, 1987-1989 (n = 7672).

	Coefficient	Standard Error (SE)	p-value
Intercept	1.17	0.013	<0.0001
Time (Baseline)	−0.038	0.0027	<0.0001
Race (Black)* Time (Baseline)	0.048	0.0062	<0.0001
Race (Black)	−0.030	0.0059	<0.0001
Age (per 1 yr)	−0.00046	0.00023	0.0485
Gender (male)	0.054	0.0025	<0.0001
High School Education (yes)	0.024	0.0034	<0.0001
Cigarette Use (yes)	−0.041	0.0032	<0.0001
High Cholesterol (yes)	−0.018	0.0031	<0.0001
Diabetes (yes)	−0.031	0.0049	<0.0001
Hypertension (yes)	−0.024	0.0029	<0.0001

Reference is White race.

Figure 2 shows mean ABI by race at each visit. After adjustment for age, gender, educational status, cigarette use, high cholesterol, hypertension and diabetes, there was a difference in ABI of 0.018 where Whites had significantly lower ABI than Blacks at baseline ($p < 0.0001$), but significantly higher (p's < 0.0001) ABI at visits 3 and 4 (ABI difference of 0.054 and 0.030, respectively). Among Whites within race analysis showed that ABI levels significantly (p's < 0.0001) increased from baseline to visit 3 and visit 4 (ABI difference of 0.042 and 0.038, respectively). In contrast, among Blacks ABI significantly decreased by a difference of 0.012 between baseline and visit 3 ($p < 0.0001$); the ABI difference of 0.0084 was not significantly lower at visit 4 ($p = 0.08$).

When effect modification between race and each covariate was tested, the only significant interaction was between race and education ($p = 0.02$). Stratification by education indicated that regardless of race, participants who had completed a high school education or more (Figure 3(a)) had higher ABI than participants *with less than a* high school education (Figure 3(b)) at follow-up visits 3 and 4; however, baseline ABI values were similar regardless of education level. Among participants *with* a high school education or more, ABI was significantly (p's < 0.0001) higher among Whites than Blacks at both follow-up visits 3 and 4 (ABI difference of 0.060 and 0.033, respectively). Among those *without* a high school education, Whites had a significantly higher ABI value of 0.039 than Blacks at the visit 3 follow-up only ($p = 0.002$) but there was no significant difference at visit 4 ($p = 0.001$).

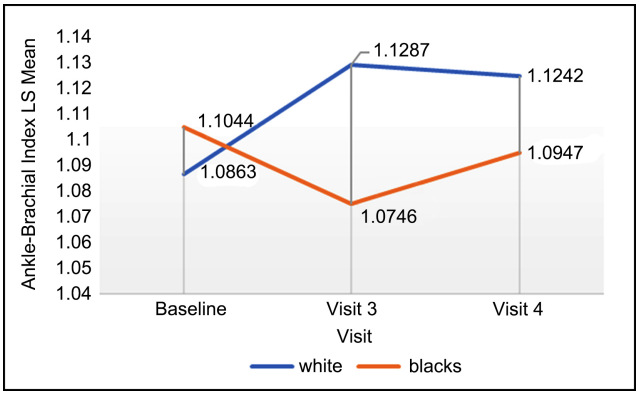
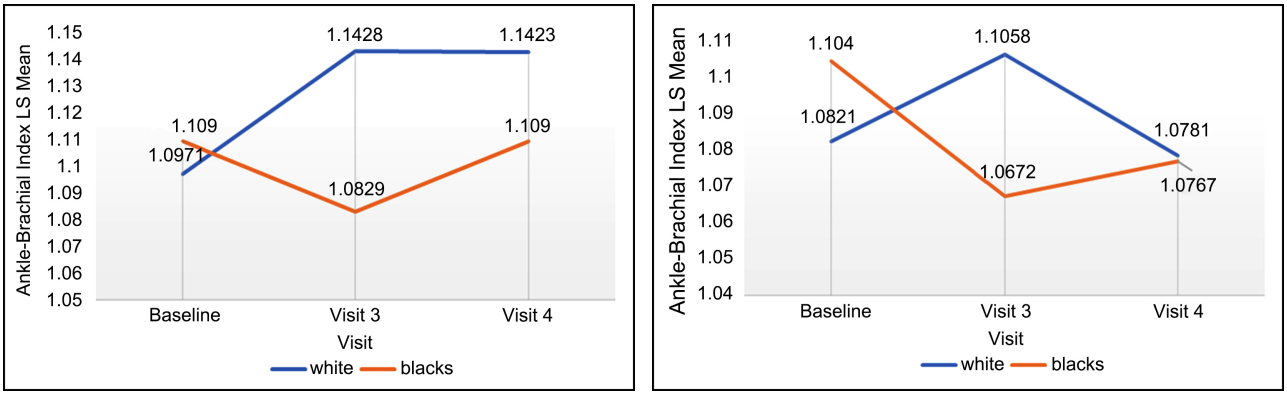


Figure 2. Race*time effects on change in ankle-brachial index (n = 7672); results of mixed-effect model repeated measures, ARIC baseline visit (1987-1989), visit 3 (1993-1995), visit 4 (1996-1998). LS Means = Least Squares Means; Model adjusted for race, age, gender, educational status, cigarette use, high cholesterol, diabetes and hypertension; time ($p < 0.0001$), race*time ($p < 0.0001$); Between race ABI change difference: Baseline ($p < 0.0001$), Visit 3 ($p < 0.0001$), Visit 4 ($p < 0.0001$); Within race ABI change for Whites: Visit 3 ($p < 0.0001$), Visit 4 ($p < 0.0001$); Within race ABI change for Blacks: Visit 3 ($p < 0.0001$), Visit 4 ($p = 0.0819$); Sample size: Baseline (Whites = 5925, Blacks = 1747), Visit 3 (Whites = 2231, Blacks = 1236), Visit 4 (Whites = 4107, Blacks = 932).



(a) (b)

Figure 3. (a) Race*time effects on change in ankle-brachial index stratified by high school graduate status (n = 6166: high school graduates); results of mixed-effect model for repeated measures, ARIC baseline visit (1987-1989), visit 3 (1993-1995), visit 4 (1996-1998). Model adjusted for race, age, gender, cigarette use, high cholesterol, diabetes and hypertension; time ($p < 0.0001$), race*time ($p < 0.0001$); Between race ABI change difference: Baseline ($p = 0.0042$), Visit 3 ($p < 0.0001$), Visit 4 ($p < 0.0001$); Within race ABI change for Whites: Visit 3 ($p < 0.0001$), Visit 4 ($p < 0.0001$); Within race ABI change for Blacks: Visit 3 ($p < 0.0001$), Visit 4 ($p = 0.9960$); Sample size: Baseline (Whites = 5053, Blacks = 1113), Visit 3 (Whites = 1901, Blacks = 787), Visit 4 (Whites = 3507, Blacks = 619); (b) Race*time effects on change in ankle-brachial index stratified by high school graduate status (n=1506: non-high school graduates); results of mixed-effect model for repeated measures, ARIC baseline visit (1987-1989), visit 3 (1993-1995), visit 4 (1996-1998). Model adjusted for race, age, gender, cigarette use, high cholesterol, diabetes and hypertension; time ($p = 0.0346$), race*time ($p < 0.0001$); Between race ABI change difference: Baseline ($p = 0.0018$), Visit 3 ($p = 0.0003$), Visit 4 ($p = 0.9000$); Within race ABI change for Whites: Visit 3 ($p = 0.0062$), Visit 4 ($p = 0.6106$); Within race ABI change for Blacks: Visit 3 ($p < 0.0001$), Visit 4 ($p = 0.0047$); Sample size: Baseline (Whites = 872, Blacks = 634), Visit 3 (Whites = 330, Blacks = 449), Visit 4 (Whites = 600, Blacks = 313).

4. Discussion

Low ABI has been associated with increased 10-year cardiovascular mortality rate in men and women suggesting that ABI screening may improve cardiovascular risk prediction [8]. In this longitudinal study, Whites had significantly higher

(better) ABI values at both follow-up visits compared to baseline than Blacks after adjustment for potentially confounding covariates. However, while these racial differences were statistically significant, the ABI differences were small (<0.15) [22] [23] and not likely to be clinically meaningful. Race, age, education, cigarette smoking, cholesterol, diabetes and hypertension were all significantly and independently associated with change in ABI over time. ABI over time was better in both Blacks and Whites who completed a high school education compared to those with less education. Among Whites without a high school education, ABI decreased and was similar to Blacks without a high school education by visit 4 of the follow-up period. While statistically significant, these ABI differences were small (<0.15) [22] [23] and therefore may not be clinically significant. Although this study did not find significant effect modification of *PON* SNPs on the association between race and ABI over time; to our knowledge this is the first study to report results of such an evaluation. Results from this study suggest that change over time in ABI by race may be modified by education or other lifestyle factors but not by genetic factors evaluated here.

Although differences may not be clinically significant, in this sample of men and women aged 45 and older, ABI was significantly lower in Blacks (1.12) than Whites (1.13) at baseline and both follow-up visits. These results are consistent with previous studies [2] [24] of 1775 healthy participants from the MESA cohort which reported that ABI values were on average, 0.02 lower in Blacks compared to non-Hispanic Whites. Furthermore, our results are also consistent with those of Singh *et al. who* reported mean ABI values of 1.11 in non-Hispanic Blacks compared to 1.13 in non-Hispanic Whites in 3348 NHANES participants [24].

The association of higher educational level and better ABI has been previously reported. Aboyans *et al.* reported a correlation between higher education and increased ABI [2]. Additionally, a separate study of the MESA cohort reported that higher education was protective against PAD [25]. Previous studies also reported an association between education and increased risk of cardiovascular disease and hypertension. In 13,948 ARIC cohort participants [26], Kubota *et al.* reported that over 50% of men and women with less than high school education had a CVD event in their lifetime as compared to 42.2% of men and 28.0% of women with some college or more. These results suggest the importance of education associated with socioeconomic status, influencing access to quality health care information and its impact on decision-making towards healthier lifestyle and better health outcomes.

The effect of education on change in ABI over time in this study suggests that ABI is influenced more by racial disparities in risk factors and their management than racial differences in the biological development of atherosclerosis. Prior studies demonstrate that racial disparities exist with Blacks receiving lower quality health care than the majority of Whites in the United States [27] [28] [29] [30] [31]. 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 diagnosis of PAD [2]. In accord with this, the present study found Black race, increasing age, cigarette smoking, high cholesterol, diabetes and hypertension were associated with decreasing ABI, trending towards PAD.

The influence of genetic differences on ABI is relatively unknown. In this analysis, there was no significant effect modification of *PON* SNPs on the association between race and change in ABI over time, and to our knowledge this is the first study to examine this issue. Paraoxonase enzymes exhibit antioxidant properties and inhibit the formation and accumulation of macrophage cholesterol, thereby ameliorating the development of atherosclerosis [32]. Some studies reported positive associations between *PON* SNPs and PAD [33], cardiovascular disease [34] and blood pressure [32] [35]. However, other studies failed to find an association between *PON* polymorphisms and stroke [36] [37] or CAD [38]. This study did not find an association between *PON* SNPs and change in ABI over time. However, because these enzyme proteins prevent oxidative stress and inflammation, improved understanding of their influence on change over time in inflammatory diseases such as atherosclerosis, merits additional research [39].

It is plausible that there is an association between race and change in ABI over time due to differences in biological risk factors. Aortic stiffening may artificially lower ABI measurements and previous studies show that Blacks have a thicker and stiffer aorta compared to Whites [5]. Among the healthy participants of the MESA cohort, Aboyans *et al.* found that Blacks had ABI values approximately 0.2 lower than Whites [2]. However, previous research by Nicoloff *et al.* and Cronenwett *et al.* reported that an ABI decrease of >0.15 over time can effectively detect significant PAD progression [22] [23]. Thus, while statistically significant, the ABI differences reported in our study were less than 0.15 and may not be clinically relevant. Future studies assessing genetic differences and gene-environment interactions with respect to change in ABI over time need to be evaluated across diverse ethnic study populations with adequate sample size [40].

Several limitations of this study were considered. 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 ABI. ABI in this study may have been underestimated due to categorization based on a single measure of systolic blood pressure from one upper and one lower extremity rather than multiple measures of all extremities. Potential bias may exist due to differences between participants included and not included in the mixed-effects model analysis (data not shown). Sensitivity analyses showed that participants included in the longitudinal analyses had higher baseline ABI, lower BMI and were younger, and more likely to be married, to have completed a high school education or more and to currently use alcohol (p's < 0.0001) than those excluded from the analyses. Those included in the longitudinal analyses were also less likely to be Black (p = 0.0008), a current smoker (p < 0.0001), or have a diagnosis of hypertension or diabetes (p's < 0.0001) than those excluded from

the analyses potentially biasing these results toward the null hypothesis.

This study also has several strengths including the use of data from a relatively large cohort of Black and White men and women who were enrolled using a standardized protocol. It also adjusted for educational level, which has been shown to contribute to differences in diagnosis and treatment. Finally, unlike previous studies, this study examined the effects of genetics as well as the interaction between race and PAD risk factors.

Conclusions: In this study, racial differences were small and while statistically significant, may not be clinically significant. Change in ABI over time differed significantly between Blacks and Whites but was modified by education. Results suggest that compared to those without a high school diploma, ABI over time is better in both Blacks and Whites who complete a high school education or more. *PON* SNPs did not modify the association between race and change in ABI over time suggesting lifestyle factors rather than genetics may modify this association. Further studies are needed to confirm these observed associations and the lack of an effect of genetics on the association between race and change in ABI over time.

Acknowledgements

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

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Supplemental

Table A. Association of SNP with ankle-brachial index (ABI) by race; screening results of univariate linear regression, ARIC, 1987-1989.

	Black	White
	p-value	p-value
***PON*1 SNPs**		
rs2057681	0.7894	0.6310
rs3917527	0.4994	0.6782
rs2301711	0.2530	0.7073
rs2299260	0.1074	0.3923
rs2299261	0.6232	0.6295
rs854568	0.3073	0.9730
rs13223537	0.0896	0.3096
rs705378	0.4722	0.4831
rs854569	0.5197	0.3072
rs17166829	0.2556	0.3584
rs3917538	0.1846	0.3160
rs3917521	0.3939	0.3671
rs854565	0.1920	0.8139
rs854566	0.2266	0.6749
rs2237583	0.3296	0.4893
rs854572	0.8074	0.1119
rs3917541	0.3908	0.9052
rs3917551	0.4133	0.7229
rs3917550	0.6240	0.9619
rs2074354	0.6937	0.1549
rs3917490	0.6534	0.7458
rs2299262	0.5749	0.6456
rs854571	0.2367	0.6101
rs13236941	0.8623	0.1334
rs2272365	0.5640	0.1252
rs705382	0.7958	0.5989
rs2269829	0.9813	0.4547
rs2299257	0.3248	0.6933

Continued

PON2 SNPs		
rs2299267	0.3821	0.2442
rs43037	0.8061	0.6057
rs7778623	0.3718	0.3284
rs43052	0.3273	0.4041
rs4729190	0.7394	0.7811
rs1557782	0.2672	0.8412
rs43063	0.4227	0.2230
rs6958904	0.2450	0.6738
rs2299263	0.2276	0.4817
rs7785039	0.8731	0.5165
rs3757707	0.7453	0.6976
rs43061	0.3288	0.3019
rs43065	0.1645	0.7556
rs2374993	0.9450	0.8512
rs10241004	0.1286	0.2341
rs10261470	0.7171	0.7718
rs10953151	0.2403	0.4992
rs6973380	0.0591	0.5017
rs10487133	0.3630	0.6179
rs7493	0.1684	0.4528
rs12534203	0.6885	0.6980
rs10953149	0.3882	0.7788
rs12535571	0.4492	0.3212
rs1639	0.4128	0.2933
rs43044	0.7834	0.7149
rs6950550	0.2243	0.0971
rs12530498	0.5771	0.1484
rs43048	0.9265	0.8929
rs7802018	0.8691	0.9285

Continued

*PON*3 SNPs		
rs468	0.8689	0.0911
rs1053275	0.3222	0.5131
rs11768074	0.6575	0.7083
rs9641162	0.4896	0.5634
rs10953143	0.1363	0.7493

References: *$p < 0.001$; ‡$p < 0.05$.