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ABO blood group is associated with peripheral arterial disease in African Americans: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Conflicts of Interest

None

Abstract

Introduction—Peripheral artery disease (PAD) affects 8.5 million Americans and thus improving our understanding of PAD is critical to developing strategies to reduce disease burden. The objective of the study was to determine the association of ABO blood type with ankle brachial index (ABI) as well as prevalent and incident PAD in a multi-ethnic cohort.

Methods—The Multi-Ethnic Study of Atherosclerosis includes non-Hispanic White, African, Hispanic, and Chinese Americans aged 45–84. ABO blood type was estimated using *ABO* genotypes in 6027 participants who had ABI assessed at the baseline exam. Associations with ABO blood type were evaluated categorically and under an additive genetic model by number of major *ABO* alleles. After excluding those with ABI>1.4, prevalent PAD was defined as ABI≤ 0.9 at baseline and incident PAD as ABI≤0.9 for 5137 participants eligible for analysis.

Results—There were 222 prevalent cases and 239 incident cases of PAD. In African Americans, each additional copy of the A allele was associated with a 0.02 lower baseline ABI (p=0.006). Each copy of the A allele also corresponded to 1.57-fold greater odds of prevalent PAD (95% CI, 1.17–2.35; p=0.004), but was not associated with incident PAD. No associations were found in other racial/ethnic groups for ABI, prevalent PAD, or incident PAD across all races/ethnicities.

Conclusions—Blood type A and the A allele count were significantly associated with baseline ABI and prevalent PAD in African Americans. Further research is needed to confirm and study the mechanisms of this association in African Americans.

Keywords

ABO blood group; ankle brachial index; atherosclerosis; peripheral arterial disease; epidemiology

1. Introduction

Peripheral artery disease (PAD) affects 8.5 million Americans [1]. Differences in the occurrence of PAD are well documented with the highest PAD prevalence in the elderly, African Americans, and women [1–4]. Furthermore, family history of PAD in a first degree relative is a strong risk factor for PAD independent of traditional risk factors [5]. Therefore, improving our understanding determinants of PAD, beyond traditional risk factors, is critical to developing strategies to reduce disease burden.

PAD typically involves the progressive reduction of blood flow to the lower extremities due to the development of atherosclerotic plaques. Atherosclerotic plaques form due to the accumulation of macrophages, cholesterol, and connective tissue in the blood vessels. Thrombus formation further impedes vascular flow [6]. Severity of PAD is associated with increased platelet activation [7]. Previous studies also reported associations between higher plasma levels of von Willebrand Factor (vWF), factor VIII, and the non-O blood groups [8–10]. Differing levels of these hemostatic factors across ABO blood groups may have an effect on the development or progression of PAD.

Several studies examined the associations between ABO blood type and PAD or intermittent claudication and reported that patients with different blood type had varying risks of lower-

extremity atherosclerosis [11–17]. However, the associations of ABO blood type with prevalent PAD and incident PAD in non-white populations is not well studied. Likewise, little is known about the associations of ankle brachial index (ABI), the major clinical diagnostic test for PAD, with blood type. To overcome these knowledge gaps, we comprehensively examined the association of ABO blood type and ABO alleles with ABI, prevalent PAD, and incident PAD in the Multi-Ethnic Study of Atherosclerosis (MESA).

2. Methods

2.1. Study participants

The Multi-Ethnic Study of Atherosclerosis (MESA) cohort included 6814 men and women aged 45–84 years and free of clinical cardiovascular disease at enrollment. Participants were enrolled from six field sites in the United States including Los Angeles County, CA (UCLA); Chicago, IL (Northwestern University); Baltimore/Baltimore County, MD (Johns Hopkins University); St. Paul, MN (University of Minnesota); Forsyth County, NC (Wake Forest University); and Northern Manhattan/Bronx, NY (Columbia University). Methods have been previously published [18]. MESA includes 2622 (38%) non-Hispanic white, 1892 (28%) African, 1493 (22%) Hispanic, and 801 (12%) Chinese American subjects with five in-person exams occurring approximately every two years from 2000–2012. The current study includes 6027 participants with ABO blood type phenotype inferred from *ABO* gene variants that had ABI assessed at Exam 1 and includes data from exams 1, 3, and 5. The study was approved by the Institutional Review Boards at each research center and informed consent was obtained from all participants.

2.2 Ankle brachial index and peripheral artery disease

Methods for the measurement of ABI were described previously [19]. In brief, ABI was measured at exams 1, 3, and 5 and calculated for both the left and right sides as maximum systolic blood pressure in the posterior tibial artery and dorsalis pedis, divided by the average of the left and right brachial pressures. In the event that left and right brachial pressures differed by 10 mmHg or more, the higher of the brachial pressures was used. If a pulse was detected when the cuff was inflated to 300 mmHg, the ABI was classified as "incompressible." All participants with an ABI > 1.4 (i.e., rigid arteries) at Exam 1 were excluded from further analysis (n = 43). Prevalent PAD was defined by Exam 1 ABI ≤ 0.9, while incident PAD was defined as ABI ≤ 0.9 at Exam 3 or 5 in individuals without PAD at baseline. Participants with incomplete data (i.e., no ABI measured at Exam 3 or 5) or participants with Exam 3 ABI > 1.4 were excluded from analysis.

2.3. Traditional peripheral arterial disease risk factors

Interview and questionnaire data were used for information on age, sex, race/ethnicity, and smoking status. Height was measured while participants were standing without shoes. Body mass index (BMI) was calculated as weight in kilograms per height in meters squared (kg/m). Blood pressure was measured three times using the Dinamap automated blood pressure device and determined by averaging the last two measurements. Triglycerides were measured in plasma by a glycerol blanked enzymatic method. Low-density lipoprotein (LDL) cholesterol was calculated in those with triglycerides <400 mg/dL using the

Friedewald formula. High density lipoprotein (HDL) cholesterol was measured using the cholesterol oxidase method after precipitation of non-HDL cholesterol with magnesium/dextran. Diabetes was defined as use of diabetes medication or insulin, or a fasting glucose ≥126 mg/dL. Hypertension was defined as use of anti-hypertensive medications, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg.

2.4. Genetic data

ABO blood type was inferred [20] based upon 28 *ABO* single nucleotide polymorphisms in 6255 MESA participants with available genetic data. Genotype data from the Illumina Exome BeadChip [21], the Illumina Cardio-MetaboChip [22], the Illumina iSelect ITMAT/Broad/CARe (IBC) Chip [23], as well as a custom Sequenom (San Diego, CA) panel, was aggregated under genome build hg19 and haplotype methods were used to estimate participant *ABO* diplotypes and corresponding allele frequencies, stratified by race/ethnicity. These diplotypes were then matched to genetic alleles from the Blood Group Antigen Gene Mutation Database (BGMUT), an online curated genetic database of *ABO* alleles [24,25]. Participants were declared to have reliable typing based upon diplotype posterior probability >0.90, resulting in 6202/6255 subjects with successful ABO typing. Each participant was assigned *ABO* genotypes of major alleles (A, B, O) as well as ABO blood type (A, B, AB, O). Population stratification was assessed using EIGENSTRAT [26] for participants with genome-wide SNP data, and first three ancestry-informative principal components (PCs) were considered for covariate adjustment.

2.5. Statistical analysis

To accommodate the truncated nature of the ABI measurements, truncated regression using the *crch* R package [27] was applied to evaluate the association between ABO blood group, ABO allele number, and Exam 1 ABI, while associations with prevalent PAD were assessed using logistic regression. Associations with incident PAD were evaluated using Cox proportional hazards regression. Event times for incident PAD were defined as the midpoint between the first exam at which ABI ≤ 0.9 and the preceding exam, and time-to-event analyses excluded all subjects with prevalent PAD (n = 222). Participants with an Exam 3 ABI and no Exam 5 ABI were considered right censored at Exam 3. A total of 92 participants had ABI measurements at Exam 5 but not at Exam 3. Of these, the 4 participants with ABI≤0.9 at Exam 5 but no ABI at Exam 3 were considered to have an event at the midpoint between Exams 1 and 5, while the remaining were assumed to be free of PAD. The assumption of proportional hazards was evaluated for all Cox regression models using a chi-square test on the Schoenfeld residuals. ABO blood type was modeled as a categorical variable with blood type O as the reference (i.e., A, B, AB, O (reference)) and ABO alleles were assessed using an additive genetic model by quantity of each major allele type (i.e., A, B, and O (reference)). For example, a subject who had AB genotype would correspond to covariate values of A = 1 and B = 1. Analyses were stratified by race/ethnicity and adjusted for age, sex, and the first three ancestry-informative PCs. Associations were declared statistically significant with a Bonferroni adjusted p-value threshold of $p < 0.05/4 = 0.01$, taking into account the number of race/ethnicity strata. Sensitivity analyses were conducted that additionally adjusted for traditional cardiovascular risk factors including smoking, diabetes, and hypertension status, BMI, total cholesterol, HDL cholesterol, and systolic

blood pressure. Interactions of race/ethnicity with ABO were evaluated by including the full cohort in the regression analysis adjusting for race/ethnicity and testing the significance of race/ethnicity-ABO interaction terms based upon a likelihood ratio test. Interactions by sex were conducted similarly within all race/ethnicity strata. All analyses were completed in the statistical software R 3.0.1.

3. Results

A total of 6027 MESA participants with ABO blood type inferred from *ABO* genotypes and had ABI assessed at Exam 1 were included in the study. Baseline characteristics by race/ethnicity are shown in Table 1 including the race/ethnicity specific distribution of blood groups. At Exam 1, 222 participants had prevalent PAD, with African Americans comprising 45% of cases (Table 2). For the 5805 participants without prevalent PAD, 5137 were eligible for the incident PAD analysis and 239 incident cases were identified during follow-up.

Table 3 summarizes the associations between ABO blood type and Exam 1 ABI by race/ethnicity. Compared to those with blood type O, blood type A was associated with lower ABI in African Americans ($\beta = -0.019$, $p = 0.014$). Association analysis by ABO allele count resulted in similar findings in African-Americans, with each additional A allele corresponding to 0.017 lower ABI ($p = 0.006$) and least square means by allele dosage commensurate with an additive model. No significant associations were identified across any of the other race/ethnicities by either blood type or blood group allele count.

Associations of ABO and prevalent PAD are presented in Table 4. We observed an increased odds of prevalent PAD in blood Type A for African (OR = 1.78; $p = 0.016$) and Chinese (OR = 5.31, $p = 0.05$) Americans. When modeling A allele dosage, increased odds of prevalent PAD for each additional A allele present was observed in African American (OR = 1.57; $p = 0.004$) and Chinese American (OR = 1.98; $p = 0.12$). In pooled analyses, each additional A allele increased the odds of prevalent PAD (OR = 1.24, $p = 0.065$) but the association appears to be driven by African Americans (race/ethnicity interaction $p = 0.064$). Furthermore, no significant interactions were observed within African Americans by sex ($p = 0.17$). In contrast, only in Hispanic Americans did we observe an increased risk of incident PAD in those with AB blood type compared to O blood type (HR = 4.97; $p = 0.01$) and ABO blood type and allele count were not significantly associated with incident PAD in the race/ethnicity pooled analyses (Table 5).

To evaluate potential differences of association between the two major A alleles (A1 and A2) and ABI, we reparameterized the A allele count into two separate variables corresponding to the respective counts of each allele. Parameter estimates for association with ABI in African Americans were comparable in magnitude and direction ($\beta_{A1} = -0.016$;$\beta_{A2} = -0.015$). No new significant associations were identified in the other race/ethnicities using these A subtypes. Additionally, adjustment for traditional risk factors did not meaningfully change the ABO association results with ABI or PAD (Supplementary Tables S1–S3).

4. Discussion

The primary goal of the current study was to investigate whether ABO blood type is associated with ABI as well as prevalent and incident PAD in a multi-ethnic cohort. Our findings suggest that blood group A and A allele count are associated with lower ABI and a 1.57 greater odds of PAD prevalence among African Americans independent of traditional PAD risk factors. In contrast, ABO blood type and *ABO* allele count were not significantly associated with ABI and prevalent PAD among Chinese, Hispanic, or non-Hispanic white Americans. Similarly, ABO blood type and *ABO* allele count were not associated with incident PAD in race/ethnicity pooled analyses.

While the relationship between ABO blood types and PAD risk has been investigated, the role of race/ethnicity remains elusive, as most previous studies have primarily focused on non-Hispanic white populations. The association between non-O blood type and PAD/intermittent claudication was first noted in the 1970's by Hall and later Kingsbury [11,15]. Subsequent to these case-control studies, the Framingham Heart Study prospectively investigated the association of ABO blood types and the development of intermittent claudication over a 10-year follow-up period and observed an increased risk in those with non-O blood types in both men and women [12]. These previous studies were limited by evaluating only subjects of European ancestry with symptomatic intermittent claudication, whereas the current study included four racial/ethnic groups exclusively with ABI measurements. In contrast, we did not observe ABO blood type associations with ABI, prevalent PAD, or incident PAD in non-Hispanic whites. Furthermore, by leveraging MESA's multi-ethnic cohort, we demonstrate that significant differences in ABI and PAD prevalence rate for blood group A compared to blood type O are exclusive to the African American population representing an independent risk factor in this group.

While there is no conclusive explanation on how ABO blood type influences PAD risk or ABI, there is evidence that the effect may be mediated by ABO antigenic determinants by blood type expressed on carbohydrate structures of vWF that are thought to influence the clearance rate of vWF [28]. Thus, the survival of vWF is longer in those with non-O blood types and circulating levels of vWF and Factor VIII release bioactive molecules under stress which have been shown to participate in the development of atherosclerosis and PAD related to endothelial dysfunction and inflammatory response [29,30]. In addition, African Americans have demonstrated higher levels of vWF and Factor VIII despite higher proportions of O blood type when compared to non-Hispanic whites and a higher prevalence of PAD compared to other race/ethnicities [3,4,31,32]. Therefore, we explored potential mediation by Factor VIII in African Americans. We found that Factor VIII is significantly associated with both A and B allele dosage, respectively corresponding to estimates of 14% ($p < 0.001$) and 34% ($p < 0.001$) increases in Factor VIII per additional allele carried. However, adjustment for Factor VIII did not attenuate the association of blood group A and lower ABI and prevalent PAD in African Americans. Likewise, prior work has shown that traditional and novel risk factors such as interleukin-6, fibrinogen, D-dimer, and homocysteine did not account for the race/ethnic specific associations with PAD [33]. Other possible explanations may include involvement of other blood antigen phenotypes that are highly represented in subjects of African descent. For example, the Duffy Fy(a-b-) null

phenotype results in the lack of Duffy antigen and is present in ~70% of African Americans, but very rare in subjects of European descent.

We demonstrated that ABO blood type was not associated with incident PAD in any of the African, Chinese, and non-Hispanic white Americans. Similar to our findings, Folsom et al., observed variations in *PCSK9* that were associated with prevalent but not incident PAD among African Americans in the Atherosclerosis Risk in Communities Study [34]. This observation may be, in part, explained by the definition of PAD that was strictly based on ABI measurements. Therefore, we conducted sensitivity analyses that included the nine additional definite and probable cases of PAD adjudicated to date to the ABI defined cases. The association results were unchanged. We also examined whether differences in the risk factor profile of prevalent verses incident subjects contributed to these findings. The supplementary Table S4 provides the comparison between groups for all major PAD risk factors that demonstrates similar risk profiles. We examined bias due to missing information and observed that after adjusting for age there was a higher chance of participant dropout at exam 3 if baseline ABI measurement between 0.9 and 0.95 ($p = 0.0002$). This finding suggests bias may be contributing to the differences in the association of ABO blood type with prevalent and incident PAD. Finally, despite similar number of prevalent and incident events ($n = 101$ *vs* $n = 95$), limited power could be an issue. Only in Hispanic Americans did we observe an increased risk of incident PAD in those with AB blood type compared to O blood type (HR = 4.97; 95% CI, 1.47–16.80, $p = 0.010$). This result should be interpreted cautiously given that of the 46 Hispanic Americans had AB blood type, 3 participants had incident PAD.

Strengths of our study include the investigation of a large multi-ethnic cohort of both men and women from four race/ethnicity groups. ABI measurement was available at 3 times over 10 years using standard methods and the MESA cohort was followed for PAD events adjudicated using standard protocols [18]. Some limitations need to be acknowledged; first, for each subsequent exam, some participants were lost to follow-up. Prior studies of blood type and PAD/intermittent claudication focused in part or whole on symptomatic patients whereas the current study used exclusively ABI measurements for the main analyses. Furthermore, PAD is rare in Chinese and Hispanic Americans and thus power may limit our ability to detect associations in stratified analyses. Although vWF was measured in a subset of 1000 MESA participants at baseline, only 173 African Americans had available ABI, ABO, and vWF data, and thus mediation analysis could not be fully explored. In general the ABO glycosyltransferase only produces A antigens, B antigens, or no antigens (blood type O), though rare ambiguous variants exist. Finally, bias arising from the fact that MESA subjects were free of CVD at baseline may have impacted our ability to detect associations.

5. Conclusions

This study showed that the ABO blood groups are associated with ABI and prevalent PAD in African Americans. Further research is needed to explore the biological mechanisms that mediate these associations and investigate reasons for differences in the association of prevalent and incident PAD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Risk of lower-extremity atherosclerosis differs by blood type.
- Type A was associated lower ankle brachial index in African Americans.
- Each copy of the A allele corresponded to 1.57-fold greater odds of PAD.

Table 1

MESA Exam 1 Characteristics by race/ethnicity, mean (standard deviation) or N (percentage).

Characteristics	African American	Chinese American	Hispanic American	Non-Hispanic White American
N	1492	741	1382	2412
Age, years	61 (10)	62 (10)	61 (10)	62 (10)
Sex (female)	808 (54)	379 (51)	721 (52)	1254 (52)
Body mass index, kg/m2	30 (6)	24 (3)	29 (5)	27 (5)
Hypertension (Yes)	884 (59)	280 (38)	575 (42)	930 (39)
Diabetes mellitus (Yes)	259 (17)	99 (13)	238 (17)	259 (17)
Total cholesterol, mg/dL	190 (36)	193 (31)	199 (38)	196 (35)
HDL cholesterol, mg/dL	52 (15)	49 (12)	48 (13)	52 (16)
LDL cholesterol, mg/dL	117 (33)	115 (29)	120 (33)	117 (30)
Triglycerides, mg/dL	105 (71)	142 (82)	158 (102)	133 (90)
Smoking status				
Never	674 (45)	555 (75)	758 (55)	1061 (44)
Former	542 (36)	145 (20)	442 (32)	1070 (44)
Current	272 (18)	41 (6)	182 (13)	280 (12)
ABO blood type				
Type A	400 (27)	192 (26)	420 (30)	1033 (43)
Type B	265 (18)	199 (27)	137 (10)	245 (10)
Type AB	77 (5)	65 (9)	33 (2)	97 (4)
Type O	750 (50)	285 (38)	792 (57)	1037 (43)

HDL: high-density lipoprotein, LDL: low-density lipoprotein.

Table 2

MESA outcomes: Mean (standard deviation) or N (percentage).

Outcome	Total MESA Cohort	African American	Chinese American	Hispanic American	Non-Hispanic White American
Exam 1, n	6027	1492	741	1382	2412
ABI	1.11 (0.11)	1.07 (0.13)	1.11 (0.09)	1.13 (0.11)	1.12 (0.11)
PAD (yes)	222 (3.7)	101 (6.8)	14 (1.9)	31 (2.2)	76 (3.2)
Exams 3 and 5, n[a]	5137	1216	640	1165	2116
Person years	41901	9576	5318	9447	17560
Incident PAD	239	95	16	46	82
Rate per 1000 person-years	5.7	9.9	3.0	4.9	4.7

ABI: ankle brachial index, PAD: peripheral arterial disease.

[a]Includes all subjects with Exam 3 and/or Exam 5 ABI measurements and free of PAD at Exam 1.

Table 3

Associations between ABO blood type and ABO allele counts and Exam 1 ABI by race/ethmcity.[a,b,c]

	Pooled Race/Ethnicity[d]			African American		Chinese American		Hispanic American		Non-Hispanic White American	
ABO Blood Type	**Beta (SE)**	**p-value**	**Interaction p-value**	**Beta (SE)**	**p-value**	**Beta (SE)**	**p-value**	**Beta (SE)**	**p-value**	**Beta (SE)**	**p-value**
O (Reference)	–	–	0.22	–	–	–	–	–	–	–	–
A	−0.002 (0.003)	0.50	–	−0.019 (0.008)	0.014	−0.007 (0.008)	0.41	0.005 (0.006)	0.43	0.003 (0.005)	0.51
B	0.000 (0.004)	0.99	–	−0.004 (0.009)	0.65	0.002 (0.008)	0.76	0.007 (0.010)	0.47	0.000 (0.008)	0.96
AB	−0.005 (0.007)	0.43	–	−0.006 (0.015)	0.72	0.010 (0.012)	0.40	−0.020 (0.019)	0.29	−0.013 (0.012)	0.28
ABO Allele Count	**Beta (SE)**	**p-value**	**Interaction p-value**	**Beta (SE)**	**p-value**	**Beta (SE)**	**p-value**	**Beta (SE)**	**p-value**	**Beta (SE)**	**p-value**
O (Reference)	–	–	0.18	–	–	–	–	–	–	–	–
A	−0.003 (0.003)	0.21	–	−0.017 (0.006)	0.006	−0.003 (0.006)	0.58	0.004 (0.005)	0.44	0.000 (0.004)	0.98
B	0.001 (0.003)	0.73	–	−0.001 (0.007)	0.93	0.003 (0.006)	0.58	0.000 (0.008)	0.97	−0.005 (0.006)	0.42

ABI: ankle brachial index, SE: standard error.

[a] ABI at Exam 1 excluding ABI > 1.4.

[b] ABI = ankle brachial index; SE = standard error

[c] Adjusted for age, sex, and leading ancestry informative PCs.

[d] Pooled analyses adjusted for race/ethnicity using PCs; Interaction tests based on self-reported race/ethnicity.

Table 4

Associations between ABO Blood Group and ABO allele counts and prevalent Peripheral Artery Disease by race/ethnicity.[a,b,c]

	Pooled Race/Ethnicity[d]			African American		Chinese American		Hispanic American		Non-Hispanic White American	
ABO Blood Type	OR (95% CI)	p-value	Interaction P-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
O (Reference)	–	–	0.079	–	–	–	–	–	–	–	–
A	1.17 (0.86,1.58)	0.32	–	1.78 (1.11,2.84)	0.016	5.31 (1.16,38.7)	0.051	0.56 (0.20,1.35)	0.23	0.80 (0.48,1.32)	0.39
B	0.67 (0.40,1.06)	0.97	–	0.62 (0.28,1.23)	0.20	2.90 (0.51,22.8)	0.25	0.22 (0.12,1.11)	0.15	0.83 (0.33,1.79)	0.65
AB	1.36 (0.69,2.47)	0.33	–	1.48 (0.49,3.70)	0.44	1.54 (0.07,18.5)	0.74	0.85 (0.42,5.26)	0.89	1.59 (0.53,3.87)	0.35
ABO Allele Count	OR (95% CI)	p-value	Interaction p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
O (Reference)	–	–	0.064	–	–	–	–	–	–	–	–
A	1.24 (0.98,1.57)	0.065	–	1.57 (1.17,2.35)	0.004	1.98 (0.83,4.70)	0.12	0.63 (0.25,1.35)	0.27	0.99 (0.66,1.43)	0.97
B	0.81 (0.56,1.14)	0.24	–	0.71 (0.40,1.17)	0.20	1.06 (0.30,3.28)	0.92	0.39 (0.61,1.31)	0.20	1.15 (0.61,1.98)	0.65

CI: confidence interval, OR: odds ratio.

[a] Prevalent PAD defined as ABI ≤ 0.9, excluding ABI > 1.4.

[b] CI = confidence interval; OR = odds ratio.

[c] Adjusted for age, sex, and leading ancestry informative PCs.

[d] Pooled analyses adjusted for race/ethnicity using PCs; Interaction tests based on self-reported race/ethnicity.

Table 5

Associations between ABO Blood Group and ABO allele counts and incident peripheral artery disease by race/ethnicity.[a,b,c]

	Pooled Race/Ethnicity[d]			African American		Chinese American		Hispanic American		Non-Hispanic White American	
ABO Blood Type	HR (95% CI)	p-value	*Interaction* p-*value*	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
O (Reference)	–	–	0.30	–	–	–	–	–	–	–	–
A	1.05 (0.78,1.41)	0.74	–	1.39 (0.86,2.26)	0.18	0.60 (0.15,2.38)	0.46	1.45 (0.74,2.85)	0.28	0.73 (0.46,1.17)	0.19
B	1.20 (0.84,1.73)	0.32	–	1.39 (0.81,2.37)	0.23	0.68 (0.20,3.66)	0.55	1.63 (0.59,3.85)	0.27	0.90 (0.44,1.87)	0.79
AB	1.08 (0.57,2.08)	0.81	–	1.24 (0.49,3.13)	0.65	0.45 (0.20,2.34)	0.45	4.97 (1.47,16.8)	0.010	0.25 (0.03,1.86)	0.18
ABO Allele Count	HR (95% CI)	p-value	*Interaction* p-*value*	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
O (Reference)	–	–	0.44	–	–	–	–	–	–	–	
A	1.02 (0.81,1.28)	0.86	–	1.16 (0.80,1.68)	0.43	0.77 (0.29,2.08)	0.61	1.38 (0.80,2.40)	0.25	0.81 (0.56,1.17)	0.27
B	1.16 (0.87,1.53)	0.31	–	1.20 (0.81,1.78)	0.36	0.67 (0.24,1.87)	0.45	1.93 (1.01,3.67)	0.045	0.84 (0.45,1.56)	0.59

CI, confidence interval; HR, hazard ratio.

[a] Incident PAD is defined as ABI ≤ 0.9 at Exam 3 or Exam 5, excluding ABI > 1.4 and prevalent PAD cases.

[b] CI = confidence interval; HR = hazard ratio.

[c] Adjusted for age, sex, and leading ancestry informative PCs.

[d] Pooled analyses adjusted for race/ethnicity using PCs; Interaction tests based on self-reported race/ethicity.