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# The Effect of Novel Cardiovascular Risk Factors on the Ethnic-Specific Odds for Peripheral Arterial Disease in the Multi-Ethnic Study of Atherosclerosis (MESA)

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**OBJECTIVES** The purpose of this study was to: 1) determine the significance and magnitude of associations between novel cardiovascular disease (CVD) risk factors and peripheral arterial disease (PAD) after adjustment for traditional risk factors; and 2) ascertain the extent to which novel risk factors explain the excess or lower risk for PAD in different ethnic groups.

**BACKGROUND** Previous reports have found a significant difference in the risk of PAD by ethnic group, with some of the risk difference attributed to different levels of traditional CVD risk factors.

**METHODS** A total of 6,814 individuals free of clinically apparent CVD were enrolled in the MESA (Multiethnic Study of Atherosclerosis) and underwent standardized testing for the presence of PAD by the ankle-brachial index. These subjects also had fasting blood drawn for serum cholesterol, glucose, and a number of novel biomarkers for CVD. Non-Hispanic whites were the largest ethnic group (38%), followed by African Americans (28%), Hispanics (22%), and Chinese (12%).

**RESULTS** In this cross-sectional analysis, 6,653 subjects with an ankle brachial index <1.40 were analyzed. The mean (SD) age was 62.2 (10.2) years, and 52.9% were women. Interleukin-6, fibrinogen, D-dimer, and homocysteine were significantly associated with PAD after adjustment for traditional CVD risk factors. Compared with non-Hispanic whites and after adjustment for traditional and "novel" risk factors, the odds for PAD were 1.47 (95% confidence interval [CI]: 1.07 to 2.02) times higher in African Americans, while being 0.45 (95% CI: 0.29 to 0.70) and 0.44 (95% CI: 0.24 to 0.78) in Hispanics and Chinese, respectively.

**CONCLUSIONS** Ethnic associations with PAD remained significant even after adjustment for traditional and novel risk factors. This suggests that unknown factors may account for the residual ethnic differences in PAD. (J Am Coll Cardiol 2006;48:1190–7) © 2006 by the American College of Cardiology Foundation

An ankle brachial index (ABI) ≤0.90 is considered abnormal and has been validated as a sensitive and highly specific marker for lower extremity atherosclerotic occlusive disease (1,2). Typically, a peripheral artery in the legs must have a cross-sectional area reduction >50% to produce a pressure drop (distal to the obstruction) sufficient to result in an abnormal ABI (3). Despite this significant atherosclerotic disease, most persons with peripheral arterial disease (PAD) do not have the classic symptom of ischemic exercise pain in the leg ("intermittent claudication") (4–6). Thus, the ABI is a more accurate tool for detecting PAD than symptoms.

Previous studies have indicated an increase in PAD prevalence with age and usually, although not uniformly, more disease in men than women (4,7,8). Several studies have indicated a higher prevalence in African Americans compared with non-Hispanic whites (7–12). Notably, 3 studies have reported ethnic-specific PAD rates in more than 2 groups (7,11,12). Using data from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2000, Selvin et al. (7) reported higher prevalence rates in African Americans and Mexican Americans compared with non-Hispanic whites. Similarly, in a study of employees and retirees from a large public university in California, compared with non-Hispanic whites, PAD rates were higher in African Americans, similar in Hispanics, and somewhat lower in Asians. Importantly, the differences in African Americans were only partially attributable to higher rates of diabetes and hypertension (12).

Several studies have indicated that cigarette smoking and diabetes are the 2 strongest risk factors for PAD (7,8,13).

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**Abbreviations and Acronyms**

ABI = ankle brachial index
AUC = area under the curve
BMI = body mass index
CHD = coronary heart disease
CI = confidence interval
CVD = cardiovascular disease
DP = dorsalis pedis
HDL = high-density lipoprotein
LDL = low-density lipoprotein
MESA = Multi-Ethnic Study of Atherosclerosis
NHANES = National Health and Nutrition Examination Survey
OR = odds ratio
PAD = peripheral arterial disease
PT = posterior tibial
ROC = receiver-operator characteristic
SBP = systolic blood pressure

Also important are hypertension and the combination of low high-density lipoprotein (HDL) cholesterol and elevated triglycerides (7,14–16). Conversely, low-density lipoprotein (LDL) cholesterol has not been shown to be a consistent risk factor for PAD (13). Whether these risk factors show the same relationships to PAD in both genders and across age and ethnic groups is currently unknown. Additionally, some studies have reported links between newer ("novel") cardiovascular risk markers and PAD. Specifically, homocysteine, C-reactive protein, interleukin-6, fibrinogen, D-dimer, and plasmin-antiplasmin complex have been reported to be linked to PAD (17–22), whereas infectious markers such as *Chlamydia pneumoniae* serology have received little attention.

Whether these new risk markers can explain a substantial amount of the ethnic differences in PAD prevalence, after adjustment for traditional cardiovascular risk factors, remains unanswered. Therefore, the aims of this study were to: 1) determine the significance and magnitude of associations between novel cardiovascular disease (CVD) risk factors and PAD after adjustment for traditional risk factors; and 2) ascertain the extent to which novel risk factors explain the excess or lower risk for PAD in different ethnic groups. We hypothesize that ethnic-specific differences in PAD prevalence will be partially, but not entirely, explained by novel risk factors.

## METHODS

**Subjects.** Details about the study design for the MESA (Multi-Ethnic Study of Atherosclerosis) have been published elsewhere (23). In brief, between July 2000 and August 2002, 6,814 men and women who identified themselves as white, African American, Hispanic, or Chinese, were 45 to 84 years old, and were free of clinically apparent CVD were recruited from portions of 6 U.S. communities: Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan and the Bronx, New York; and St. Paul, Minnesota. Each field site recruited from locally available sources, which included lists of residents, lists of dwellings, and telephone exchanges. In the last few months of the recruitment period, supplemental sources (lists of Medicare beneficiaries from the Centers for Medicare and Medicaid Services and referrals by participants) were used to ensure adequate numbers of minorities and elderly subjects. Individuals with a history of physician-diagnosed heart attack, angina, heart failure, stroke, or transient ischemic attack, or having undergone an invasive procedure for CVD (coronary artery bypass grafting, angioplasty, valve replacement, or pacemaker placement) were excluded from participation. The institutional review boards at all participating centers approved the study, and all participants gave informed consent.

**Data collection.** Standardized questionnaires were used to obtain demographic and information about 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 3 times in seated participants with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Wipro GE Healthcare, Waukesha, Wisconsin). The average of the last 2 measurements was used in analysis. Hypertension was defined as systolic pressure $\geq$140 mm Hg, diastolic pressure $\geq$90 mm Hg, or current use of antihypertensive medication.

**Laboratory.** Blood was collected and stored at −70°F until needed for the appropriate assays. Total and HDL cholesterol, triglycerides, and glucose levels were measured from blood samples obtained after a 12-h fast; LDL cholesterol was calculated with the Friedewald equation (24). The total cholesterol/HDL cholesterol ratio was considered abnormal if it was >5.0 or if the participant used medication to reduce cholesterol ("dyslipidemia"). Diabetes was defined as fasting glucose $\geq$126 mg/dl or use of hypoglycemic medication. Impaired fasting glucose was defined as fasting glucose 100 to 125 mg/dl (25).

In addition to the previously listed indexes, fasting blood was collected for the following categories of analytes: lipids, systemic inflammation (high-sensitivity C-reactive protein, fibrinogen, interleukin-6), insulin concentration (fasting insulin), infectious agents (*C. pneumoniae* antibody titer), hemostasis/fibrinolysis (factor VIII, plasmin-antiplasmin complex, D-dimer), as well as homocysteine and von Willebrand factor. Of note, von Willebrand factor was collected in a random sample of 1,000 subjects instead of the entire cohort.

**ABI protocol.** After the participant rested supine for 5 min, systolic blood pressure (SBP) was measured in both arms with the appropriate-sized arm cuff. For each leg, the

SBP in each posterior tibial (PT) and dorsalis pedis (DP) artery was measured. All pressures were detected with a continuous-wave Doppler ultrasound probe. The leg-specific ABI was calculated as the higher SBP in the PT or DP divided by the higher of the 2 arm SBPs. The highest arm SBP was used because of the strong association between PAD and subclavian stenosis (26). For each subject, PAD was defined by an ABI ≤0.90 in either leg.

**Statistical analysis.** This was a cross-sectional analysis of data collected at the baseline visit. Chi-square tests were used to assess unadjusted associations between the presence of PAD and ethnicity. Logistic regression models were used to assess adjusted associations. In each model, the following traditional cardiovascular risk factors were forced into the model in addition to ethnicity: age, gender, BMI, diabetes, current smoking, hypertension, and HDL and LDL cholesterol. To assess whether the newer risk factors explained some of the ethnic differences, we forced these into the model including the traditional risk factors, and examined the changes in the ethnicity odds ratios (OR), significance, and the area under the receiver-operator characteristic (ROC) curve. In all of the previously mentioned models, those with an ABI >1.4 in 1 or both legs and a normal ABI in the other leg (if applicable) were excluded due to possible arterial stiffness and thus the inability to accurately assess PAD (26). Interactions between all traditional and novel risk factors with ethnicity were examined.

## RESULTS

The baseline characteristics of the MESA cohort have been published previously (27). After excluding 161 subjects with either an ABI >1.40 or missing data for this variable, 6,653 subjects remained for this cross-sectional analysis. Overall, the mean (SD) age was 62.2 (10.2) years, and 52.9% were women. Ages ranged from 45 to 85 years with the majority (60%) being between 50 and 69 years. Non-Hispanic whites were the largest ethnic group (38%), followed by African Americans (28%), Hispanics (22%), and Chinese (12%). A total of 14% were diabetic, 13% were current smokers, 34% had dyslipidemia, and 44% were classified as hypertensive.

The baseline characteristics of the cohort stratified by ABI category are presented in Table 1. Subjects with an ABI ≤0.90 were significantly older and had higher levels of all novel risk factors except von Willebrand factor and titer positivity for *C. pneumoniae*. Furthermore, the proportion with diabetes, smoking, hypertension, dyslipidemia, low income (<$25,000), and lower education level (≤ high school) were significantly higher in those with PAD.

Table 2 provides the age- and gender-adjusted means and proportions for the independent variables stratified by ethnicity. There were significant ethnic differences in all traditional and novel risk factors. Compared with non-Hispanic whites, African Americans had significantly worse risk factor levels with the exception of a lower prevalence of dyslipidemia. This included much higher prevalences of diabetes, current smoking, hypertension, less education and income, and higher average values of BMI and the novel analytes. Hispanics had worse traditional risk factors compared with non-Hispanic whites, including a higher prevalence of dyslipidemia. Conversely, Chinese had the same or better average levels of all risk factors compared with whites with the exception of a higher prevalence of diabetes, and less education and income.

Overall, the prevalence of PAD increased substantially with age, such that the rate was 1.3% for those 44 to 49 years and increased to 9.3% for those over the age of 70. Although the mean ABI was significantly lower in women than in men (1.08 vs. 1.13, $p < 0.01$), the prevalence with an ABI ≤0.90 was the same in both genders (4.2 vs. 4.1%, respectively, $p = 0.8$), a finding that was consistent across different age categories (44 to 49, 50 to 59, 60 to 69, ≥70) and all ethnic groups. Notably, African Americans had a substantially higher prevalence of PAD (7.2%) compared with non-Hispanic whites (3.6%), Hispanics (2.4%), and Chinese (2.0%) ($p < 0.01$ for overall ethnicity association). There were also differences by diabetes classification. Participants with diabetes had the highest PAD prevalence (8.7%), whereas the rate was 4.2% in those with impaired fasting glucose and 3.0% for individuals with a normal fasting glucose. For current smokers, PAD prevalence was 7.7%; former smokers, 4.4%; and never smokers, 3.0%.

In a multivariable logistic model consisting of age, gender, and ethnicity, each 1-year increment in age was associated with a 10% greater odds of PAD ($p < 0.01$). There was no significant interaction between gender and ethnicity for PAD. Compared with non-Hispanic whites, African Americans were found to have over twice the odds of an ABI ≤0.90 (OR = 2.28, $p < 0.01$) whereas Chinese had significantly lower odds (OR = 0.56, $p = 0.03$). The odds for Hispanics were also lower (OR = 0.74), but this result was not statistically significant ($p = 0.14$). The area under the curve (AUC) associated with the ROC analysis of this model (age, gender, and ethnicity) was 0.77. The addition of diabetes, pack-years of cigarette smoking, hypertension, dyslipidemia, BMI, education, and income levels increased the AUC to 0.81 ($p < 0.01$, compared with previous model). Notably, with adjustment for these risk factors, the ORs were altered for all 3 ethnic groups: African American: OR = 1.67, Chinese: OR = 0.39, and Hispanic: OR = 0.49, with all being statistically significant (Table 3). When the summary variable for diabetes in the aforementioned multivariable model was replaced by a variable that used 3 categories based on fasting glucose levels, participants with impaired fasting glucose had an 87% higher odds of PAD ($p = 0.02$). Similarly, each 1-mU/l increment in fasting serum insulin was associated with a 29% higher odds for PAD, but the addition of this variable did not improve the ability of the model to discriminate the presence or absence of an ABI ≤0.90 (AUC = 0.81, p = NS).

Table 4 provides the results of adjusted associations between novel risk factors and PAD. In general, there was

**Table 1.** Cohort Characteristics and Differences in Risk Factors by ABI Category

| Traditional Risk Factors | Low ABI (≤0.9) (n = 275) | Normal ABI (0.91–1.4) (n = 6,378) | p Value* |
|---|---|---|---|
| Age (yrs) | 70 ± 9 | 62 ± 10 | <0.01 |
| Female gender | 149 (54.2) | 3,397 (53.3) | 0.76 |
| Ethnicity | | | <0.01 |
| Non-Hispanic white | 91 (3.6) | 2,461 (96.4) | |
| Chinese | 16 (2.0) | 780 (98.0) | |
| African American | 133 (7.2) | 1,720 (92.8) | |
| Hispanic | 35 (2.4) | 1,417 (97.6) | |
| Diabetes | | | <0.01 |
| Normal diabetes status | 117 (3.0) | 3,733 (97.0) | |
| Impaired fasting glucose | 77 (4.2) | 1,773 (95.8) | |
| Untreated diabetes status | 18 (6.3) | 266 (93.7) | |
| Treated diabetes status | 63 (9.8) | 582 (90.2) | |
| Fasting insulin (mU/l) | 7.9 ± 9.8 | 6.8 ± 5.3 | <0.01 |
| Smoking | | | <0.01 |
| Never smoker | 99 (3.0) | 3,245 (97.0) | |
| Former smoker | 107 (4.4) | 2,295 (95.6) | |
| Current smoker | 67 (7.7) | 803 (92.3) | |
| BMI (kg/m$^2$) | 28.0 ± 5.5 | 28.3 ± 5.4 | 0.28 |
| Hypertension (yes) | 195 (70.9) | 2,747 (43.1) | <0.01 |
| Dyslipidemia (yes) | 127 (46.2) | 2,128 (33.5) | <0.01 |
| Education | | | <0.01 |
| <High school | 65 (5.5) | 1,125 (94.5) | |
| High school | 69 (5.7) | 1,131 (94.3) | |
| College | 111 (3.6) | 2,937 (96.4) | |
| Grad school | 28 (2.3) | 1,165 (97.7) | |
| Income | | | <0.01 |
| <$25,000 | 121 (6.1) | 1,879 (93.9) | |
| $25,000–$49,999 | 71 (3.8) | 1,781 (96.2) | |
| $50,000–$99,999 | 34 (2.0) | 1,635 (98.0) | |
| $100,000 or more | 21 (2.4) | 842 (97.8) | |
| Novel risk factors | | | |
| Homocysteine (μmol/l) | 10.9 ± 4.4 | 9.2 ± 3.5 | <0.01 |
| C-reactive protein (mg/l) | 5.4 ± 7.9 | 3.7 ± 5.7 | <0.01 |
| Interleukin-6 (pg/ml) | 2.1 ± 1.6 | 1.5 ± 1.2 | <0.01 |
| D-dimer (μg/ml) | 0.6 ± 0.9 | 0.4 ± 0.8 | <0.01 |
| Fibrinogen (mg/dl) | 383 ± 80 | 345 ± 73 | <0.01 |
| Plasmin-antiplasmin (nmol/l) | 6.0 ± 3.6 | 4.7 ± 2.1 | <0.01 |
| Factor VIII (%) | 181 ± 67 | 163 ± 66 | <0.01 |
| von Willebrand factor (%) | 157 ± 54 | 138 ± 57 | 0.08 |
| *Chlamydia pneumoniae* titer positive | 221 (80.4) | 4,783 (75.3) | 0.06 |

*Comparing low with normal ankle brachial index (ABI). Values expressed as mean ± SD or n (%).
BMI = body mass index.

a decrease in the magnitude of the OR for PAD for all of the novel risk factors when adjusted for: 1) age, gender, and ethnicity ("model 1"); then 2) model 1 + the traditional risk factors ("model 2"); and then 3) model 2 + the other novel risk factors ("model 3"). When analyzed individually and with adjustment for traditional CVD risk factors, all novel risk factors were positively associated with PAD except *C. pneumoniae* ($p = 0.63$) and factor VIII ($p = 0.58$). In a model including all novel and traditional risk factors ("model 3"), interleukin and fibrinogen were significantly associated with PAD ($p < 0.05$ for all), whereas homocysteine and D-dimer were of borderline significance ($0.05 < p < 0.10$). Notably, in a model containing interleukin-6, C-reactive protein, and the traditional risk factors, interleukin-6 remained significant, but C-reactive protein did not. Therefore, in a "final" model adjusted for traditional risk factors and all significant novel risk factors, 1-SD increments in interleukin-6, fibrinogen, D-dimer, and homocysteine were associated with 32%, 23%, 18%, and 16% higher odds for PAD, respectively ($p < 0.05$ for all). The AUC for this final model was 0.84 ($p < 0.01$).

With the addition of these novel risk factors, the ORs for PAD by ethnic group remained significantly associated with PAD. Specifically, with adjustment for age, gender, ethnicity, traditional, and novel risk factors, the OR for PAD in African Americans decreased to 1.47 (95% confidence interval [CI]: 1.07 to 2.02) but remained essentially unchanged in Hispanics (OR = 0.45, 95% CI: 0.29 to 0.70) and Chinese (0.44, 95% CI: 0.24 to 0.78). To facilitate comparison of the effects of different categories of risk factors on the ethnicity-specific odds for PAD, Figure 1 provides the odds for PAD by ethnicity after adjustment for: 1) age, gender,

**Table 2.** Age- and Sex-Adjusted Means and Proportions of Risk Factors by Ethnic Group

| | African American (n = 1,863) | Chinese (n = 798) | Hispanic (n = 1,464) | Non-Hispanic White* (n = 2,528) |
|---|---|---|---|---|
| Traditional risk factors | | | | |
| Body mass index (kg/m$^2$) | 30.1† | 24.0† | 29.4† | 27.8 |
| Current smoking (%) | 17.0† | 5.0† | 12.0 | 10.8 |
| Diabetes (%) | 19.1† | 14.5† | 19.3† | 6.7 |
| Dyslipidemia (%) | 29.4† | 32.0 | 38.3† | 34.3 |
| Hypertension (%) | 59.5† | 35.5 | 41.6† | 36.0 |
| Education‡ (%) | 69.2† | 59.4† | 33.1† | 79.3 |
| Gross income ≥$25,000 (%) | 65.3† | 50.1† | 47.5† | 84.2 |
| Novel risk factors | | | | |
| *Chamydia pneumoniae* titer positive (%) | 81.4† | 86.0† | 75.6† | 69.1 |
| C-reactive protein (mg/l) | 4.8† | 1.9† | 4.2† | 3.4 |
| D-dimer (μg/ml) | 0.45† | 0.27† | 0.38 | 0.35 |
| Factor VIII (%) | 177.8† | 157.6 | 162.9† | 156.5 |
| Fibrinogen (mg/dl) | 360.6† | 329.6 | 360.6† | 334.4 |
| Homocysteine (μmol/l) | 9.7† | 8.9† | 9.1 | 9.3 |
| Interleukin-6 (pg/ml) | 1.7† | 1.1† | 1.7† | 1.5 |
| Plasmin-antiplasmin (nmol/l) | 5.2† | 4.1† | 4.7 | 4.7 |
| von Willebrand factor (%) | 160.0† | 142.9 | 142.0 | 137.1 |

*Reference group; †p value <0.05 compared with non-Hispanic white; ‡Greater than high school.

and ethnic group; 2) model 1 + smoking, diabetes, hypertension, dyslipidemia, BMI, education, and income; and 3) model 2 + interleukin-6, fibrinogen, D-dimer, and homocysteine.

## DISCUSSION

In this large, cross-sectional study of participants from varying geographic locations and ethnic origins, the relative odds of PAD, compared with non-Hispanic whites, were significantly elevated in African Americans but were reduced in Chinese and Hispanics. Compared with non-Hispanic whites and after adjustment for traditional and novel coronary heart disease (CHD) risk factors, African American ethnicity was associated with nearly a 50% increase in the odds of PAD. Conversely, Chinese and Hispanic ethnicities were associated with approximately half the odds for this condition. Importantly, in African Americans, adjustment for demographic, traditional, and novel risk factors accounted for an important proportion of the unadjusted risk. Conversely, after adjustment the inverse association for Hispanic ethnicity was greatly enhanced and somewhat enhanced in Chinese. This suggests that elevations in these risk factors in Hispanics and Chinese made the overall risk appear to be closer to that of non-Hispanic whites.

Recent reports from the NHANES have estimated the overall burden of PAD in the U.S. using ABI criteria at approximately 5 million individuals (4.3%) (7,8). In the NHANES, the prevalence of PAD in non-Hispanic whites was 4.4%. From community-based samples that included individuals under the age of 65, the higher prevalence of PAD in African Americans has been well documented with unadjusted overall prevalences ranging from 3.3% to 7.9% (7,10,12), which are similar to that found in MESA (7.2%). Notably, prevalence estimates for Hispanics and Asians are more limited. Three reports have provided rates in Hispanics (1.8%, 3.0%, and 13.7%) (7,11,12), whereas there is only 1 study reporting the prevalence in Asians that included subjects under the age of 70 years (1.4%) (12). These rates are all comparable to those found in MESA—Hispanics: 2.4% and Asians: 2.0%.

**Table 3.** Traditional Risk Factors for PAD

| Model #1 | Odds Ratio | 95% CI |
|---|---|---|
| Age (1 yr) | 1.10 | 1.08–1.11 |
| Gender (male) | 0.99 | 0.77–1.27 |
| Ethnicity | | |
| Non-Hispanic white | 1.00 | — |
| Chinese | 0.56 | 0.32–0.96 |
| African American | 2.28 | 1.72–3.01 |
| Hispanic | 0.74 | 0.50–1.10 |
| **Model #2** | | |
| Age (1 yr) | 1.09 | 1.07–1.11 |
| Gender (male) | 0.95 | 0.73–1.23 |
| Ethnicity | | |
| Non-Hispanic white | 1.00 | — |
| Chinese | 0.39 | 0.22–0.69 |
| African American | 1.67 | 1.23–2.26 |
| Hispanic | 0.49 | 0.32–0.76 |
| Diabetes mellitus | 2.12 | 1.57–2.87 |
| Smoking | 3.42 | 2.48–4.73 |
| Hypertension | 1.63 | 1.22–2.18 |
| Dyslipidemia | 1.58 | 1.22–2.05 |
| Body mass index | 0.97 | 0.94–0.99 |
| Education* | 0.74 | 0.55–0.98 |
| Income† | 0.75 | 0.56–1.01 |

Model 1: adjusted for age, gender, and ethnicity; model 2: adjusted for age, gender, ethnicity, diabetes, smoking, hypertension, dyslipidemia, body mass index, education, and income. *Greater than high school compared with high school or less; †greater than $25,000 compared with less than this amount.

CI = confidence interval; PAD = peripheral arterial disease.

**Table 4.** Odds of PAD Associated With a 1-SD Increment in Each Novel Risk Factor

| Novel Risk Factors | Model 1 OR (95% CI) | Model 2 OR (95% CI) | Model 3 OR (95% CI) |
|---|---|---|---|
| LN homocysteine (μmol/l) | 1.25 (1.10–1.41) | 1.15 (1.02–1.31) | 1.13 (0.99–1.30) |
| LN C-reactive protein (mg/l) | 1.31 (1.15–1.49) | 1.29 (1.12–1.49) | 1.02 (0.85–1.22) |
| LN interleukin-6 (pg/ml) | 1.53 (1.34–1.75) | 1.47 (1.28–1.70) | 1.29 (1.08–1.53) |
| LN D-dimer (μg/ml) | 1.35 (1.19–1.54) | 1.29 (1.12–1.48) | 1.15 (0.98–1.34) |
| Fibrinogen (mg/dl) | 1.38 (1.23–1.55) | 1.31 (1.16–1.48) | 1.18 (1.01–1.39) |
| LN plasmin-antiplasmin (nM) | 1.29 (1.13–1.48) | 1.29 (1.12–1.47) | 1.11 (0.94–1.30) |
| Percent factor VIII | 1.07 (0.95–1.21) | 1.01 (0.88–1.16) | 0.96 (0.83–1.09) |
| *C. pneumoniae* titer positive (%) | 1.04 (0.90–1.19) | 1.03 (0.91–1.16) | 0.99 (0.86–1.15) |

Model 1: adjusted for age, gender, and ethnicity; model 2: adjusted for age, gender, ethnicity, diabetes, smoking, dyslipidemia, hypertension, body mass index, education, and income; model 3: adjusted for those in model 2 and the other novel risk factors. LN = log transformed; OR = odds ratio; other abbreviations as in Table 3.

Similar to the findings presented in the preceding text, after adjusting for age, gender, smoking, BMI, hypertension, hypercholesterolemia, diabetes, and kidney function, African American subjects from the NHANES had a significantly higher odds (2.39) for PAD than non-Hispanic whites (7). Conversely, and unlike our MESA results, the OR for Mexican Americans was elevated, but not significantly (1.15; 95% CI: 0.6 to 2.2). After controlling for traditional CHD risk factors, a study of university employees reported that African Americans had a significant 2.3-fold higher odds of PAD compared with non-Hispanic whites, whereas Hispanics had 8% higher and Asians a 38% lower odds, neither of which was statistically significant (12). Finally, in the GENOA (Genetic Epidemiology Networks of Arteriopathy) study, African Americans were again found to be at higher odds for PAD independent of traditional CHD risk factors. Because these results suggest that traditional risk factors did not account for the risk for PAD in different ethnic groups, the authors recommended "identifying additional 'novel' risk factors that account for the ethnic differences in PAD. . ." (28).

Accordingly, we determined the significance and magnitude of associations between novel risk factors and PAD. Of the 9 studied, 4 were significantly associated with PAD after adjustment for age, gender, ethnicity, smoking, diabetes, hypertension, dyslipidemia, and BMI: interleukin-6, fibrinogen, D-dimer, and homocysteine. Using standardized differences, 1-SD increments in interleukin-6 were associated with the largest odds for PAD (1.32), followed by fibrinogen (1.23), D-dimer (1.18), and homocysteine (1.16). C-reactive protein, plasmin-antiplasmin, factor VIII, von Willebrand factor, and a positive antibody titer for *C. pneumoniae* were not significantly associated with PAD. This study also demonstrated a significant risk factor–adjusted association for impaired fasting glucose (OR = 1.87), as well as fasting serum insulin (1.29 per 1-SD increment) with PAD. Notably, the addition of the novel risk factors increased the AUC from 0.81 (for traditional risk factors alone) to nearly 0.84, indicating some increase in the ability to discriminate between those with and without PAD. The inclusion of either impaired fasting glucose or serum insulin did not increase the AUC on ROC analysis.

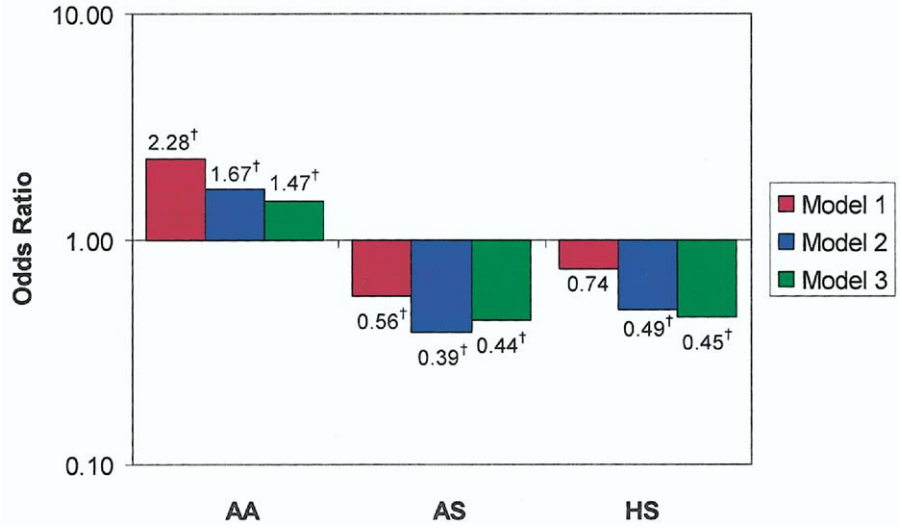


**Figure 1.** *Ethnic-specific odds ratios for peripheral arterial disease. *Non-Hispanic white = reference group; †$p < 0.05$. AA = African American; AS = Chinese; HS = Hispanic. Model 1 = adjusted for age and gender; model 2 = adjusted for those in model 1 + diabetes, smoking, hypertension, dyslipidemia, body mass index, education, and income; model 3 = adjusted for those in model 2 + interleukin-6, fibrinogen, D-dimer, and homocysteine.

In previous studies, levels of fibrinogen, von Willebrand factor, and D-dimer have been shown to be higher in patients with PAD as determined by a low ABI (<0.9) (29). Furthermore, studies of different age groups have found fibrinogen to be significantly associated with not only prevalent (30) but incident (31) PAD after adjustment for traditional CHD risk factors, and this increased risk may be genetically mediated (32). Notably, associations with homocysteine are less consistent (31,33,34). Importantly, there are insufficient data available in published reports to determine if there is an interaction between novel risk factors and ethnicity for PAD. We did not observe any such interactions in this study (data not shown).

In MESA, the addition of novel risk factors to a model adjusted for traditional CHD risk factors resulted in a substantial change in the relative odds for PAD among African Americans but not in Hispanics and Chinese. Even after adjustment for the novel risk factors, ethnicity remained independently associated with PAD, and the magnitude of associations are clinically meaningful (i.e., nearly a 50% increased OR for African Americans and approximately half the odds in Chinese and Hispanics compared with non-Hispanic whites). These results suggest that the novel risk factors studied do not entirely explain the difference in ethnic-specific odds for PAD. Therefore, study of either additional "novel" risk factors (such as lipoprotein (a) and plasminogen activator inhibitor-1) (35) or genetic markers of PAD risk are warranted.

Interestingly, in previous studies from this same cohort, the prevalence of coronary calcium is lower in African Americans, Hispanics, and Chinese (27). For African Americans, our results contrast with those for the presence of calcium in the coronary arteries. This suggests that there is either an arterial bed-specific ethnic atherosclerotic predilection, or that rates of calcification of atherosclerotic plaques differ by ethnicity.

Our study has limitations, and thus our conclusions are drawn with caution. First, the selection of subjects, although population-based, was not random and, by design, excluded subjects with clinical CVD. Thus, some selection bias was possible. Second, the number of cases of PAD in Chinese and Hispanics was relatively small. However, the denominators for these ethnic groups were relatively large, giving reasonable confidence in the low PAD rates in these 2 ethnic groups. Finally, residual confounding due to misclassification and non-perfect ascertainment of risk factors likely led to an overestimation of the independent effect of African-American ethnicity on risk but, by the same token, may have led to an underestimation of the independent effects of Hispanic and Chinese ethnicity.

**Conclusions.** Traditional and novel CHD risk factors account for some of the differences in the prevalence of PAD in African American, Hispanic, and Chinese ethnicities versus Caucasians. However, the ethnic differences in the odds of PAD remained significant even after adjustment for these risk factors. This suggests that either intrinsic risk factors associated with ethnicity, mediators other than those studied, or different durations of risk factor elevations account for the ethnic differences in the odds for PAD.

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