Intrinsic contribution of gender and ethnicity to normal ankle-brachial index values: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Objective: **Several studies report a higher prevalence of peripheral arterial disease (PAD) in women and among blacks. These studies based their PAD definition on an ankle-brachial index (ABI) <0.90. We hypothesized that there is an inherent contribution of gender and ethnicity to normal ABI values, independent of biologic and social disparities that exist between gender and ethnic groups. Consequently, an ABI threshold that disregards these fundamental gender-related and ethnicity-related differences could partly contribute to reported prevalence differences.**

Methods: **A cross-sectional study was designed as part of the Multi-Ethnic Study of Atherosclerosis (MESA), a multicenter United States population study. We selected a subgroup of participants with unequivocally normal ABIs (1.00 to 1.30), and additionally excluded participants with any major PAD risk factor (smoking, diabetes, dyslipidemia, hypertension). In a linear model with ABI as the dependent variable, demographic, clinical, biologic, and social variables were introduced as independent factors.**

Results: **Among 1775 healthy participants, there was no association between ABI level and subclinical cardiovascular disease (coronary calcium or carotid plaque). Male gender, weight, and high education level were positively correlated with ABI, whereas black race, triglycerides, pack-years (in past smokers), and pulse pressure were negatively correlated. In the fully adjusted model, women had about 0.02 lower ABI values than men, and blacks showed ABI values about 0.02 lower than non-Hispanic whites.**

Conclusion: **These data suggest intrinsic ethnic and gender differences in ABI. Such differences, although small in magnitude, are highly significant and can distort population estimates of disease burden. (J Vasc Surg 2007;45:319-27.)**

As a manifestation of atherosclerosis, peripheral arterial disease (PAD) is associated with lower extremity functional limitations, trophic complications, and an increased risk for future cardiovascular events.[1-6] Beyond older age and male gender, the major risk factors contributing to this condition are smoking, diabetes, and to a lesser degree, hypertension and dyslipidemia.[7,8] Because it also allows the detection of asymptomatic subjects, epidemiologic studies in the last 20 years have typically based their definition of PAD on the ankle-brachial index (ABI).[3,5,6,8-15] Even at a subclinical level, the presence of PAD defined by an abnormal ABI is a reliable marker of future cardiovascular events.[1-3,5,6] Hence, ABI measurement is of great clinical relevance for the diagnosis of PAD as well as for the assessment of cardiovascular risk.[1,8]

Recent estimates[16,17] report a prevalence of 5 to 7 million adults in the United States population with PAD, with higher rates among blacks compared with non-Hispanic whites (NHWs). Despite the analysis of several biologic and socioeconomic factors, this difference has not been fully explained.[11,13,16,18-21] More surprisingly, several community-based surveys[9,11,13,21] report higher rates of PAD in women compared with men, even after adjusting for age.[11,21] This contrasts with what is generally accepted about the prevalence of atherosclerotic diseases, where women, especially until the seventh decade, present a lower rate of cardiovascular diseases (CVD).[22]

Because the prevalence of PAD among gender and ethnic groups is usually defined by a low ABI (<0.90), one might question whether ABI values in health are similar within gender/ethnic groups and whether a single threshold for all gender/ethnic groups is then appropriate. An earlier epidemiologic study reported lower

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Competition of interest: none.

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ABI values in healthy women than men.[23] It is not obvious whether different ABI values observed in gender/ethnic groups are actually related to differences in the development of atherosclerosis in the lower limbs, or whether some intrinsic anatomic or physiologic differences could partly affect these values. In a whole population, after adjusting for different prevalence in CVD risk factors in gender and ethnic groups, residual confounding and other biases might remain (eg, risk factor management disparities between genders or across ethnic groups). Thus, to assess potential intrinsic differences in ABI values appropriately, a healthy population free of PAD and its modifiable risk factors is required.

In this cross-sectional study, focused on subjects free of PAD, we hypothesized that even after adjustment for biologic and social disparities between gender and ethnic groups, an independent effect of these two characteristics on the ABI would remain. If such a fundamental difference between genders and ethnic groups existed, it might influence the gender and ethnic group disparities in PAD prevalence reported in the general population when a single ABI threshold is used. The Multi-Ethnic Study on Atherosclerosis (MESA) provided a unique opportunity to explore this hypothesis.

MATERIALS AND METHODS

Multi-Ethnic Study on Atherosclerosis population. MESA was initiated by the National Heart, Lung and Blood Institute to investigate the prevalence, correlates, and progression of subclinical CVD in a multiethnic population-based sample of 6814 men and women aged 45 to 84 years without a history of clinical CVD.[24] Participants were selected between 2000 and 2002 from six United States field centers: 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. The Institutional Review Boards at all participating centers approved the study, and all participants gave informed consent. The study was designed to include 38% NHWs, 28% blacks, 23% Hispanics, 11% of Chinese descent, and approximately 50% women.

Study population (the healthy group). To determine the correlates of normal ABI values, we first defined a subset of the MESA population with no evidence of PAD. The normal range of ABI used as a starting point was between 1.00 and 1.30. This was based on a previous MESA publication showing a correlation with subclinical coronary and carotid disease when ABI was <1.00 or >1.30.[25] Because a normal ABI does not definitely exclude the presence of PAD,[16,26] we also excluded from the normal ABI group all participants at high risk of PAD based on the presence of any major risk factor. Participants were excluded if they were diabetic, hypertensive, a smoker, or had dyslipidemia (defined in the next section). According to these criteria, 1775 participants without any major risk factor and an ABI of 1.00 to 1.30 constituted the healthy PAD-free subgroup.

Definition of major risk factors. Participants were considered smokers if they reported current cigarette smoking or had stopped smoking within the last 2 years. Dyslipidemia was defined by a total/high-density-lipoprotein cholesterol ratio >5 or use of lipid-lowering agents.[27] Diabetes was defined by fasting blood glucose >1.26 g/L or use of antidiabetic drugs.

Systolic and diastolic blood pressures (SBP, DBP) were measured three times in the right arm of seated participants with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, FL). The average of the last two measurements was used in the analyses. Participants were considered hypertensive if SBP was >140 mm Hg or DBP >90 mmHg, or both, or the subject both self-reported a history of hypertension and was taking antihypertensive drugs. We also analyzed the respective contributions of the steady and pulsatile components of blood pressure,[28] expressed as the mean blood pressure (MBP = 2/3 DBP + 1/3 SBP) and the pulse pressure (PP = SBP – DBP).

Laboratory variables. Laboratory variables were centrally measured on blood collected from enrollees and frozen at –70°C. The methods of measurements are described elsewhere.[23]

Ankle-brachial index. After a 5-minute rest in a supine position, SBPs were measured in both arms and in the posterior tibial (PT) and dorsalis pedis (DP) arteries of both ankles, using appropriate-sized cuffs and a continuous wave Doppler probe. The ABI was computed separately for each leg, with the numerator the highest of the PT or DP systolic pressures and the denominator the highest of the right vs left brachial systolic pressures. The index ABI for the participant was the lower of the right vs left ABI.

Subclinical disease measures. Computed tomography imaging of the coronary arteries was performed as previously described.[24,29,30] We defined the presence of subclinical coronary disease by the presence of any coronary calcification (CAC score >0). Carotid ultrasound imaging protocol has been described elsewhere.[24,25] The images were analyzed off-line for the presence of carotid plaque, defined as any focal thickening of the carotid wall in the carotid bulbs or internal carotid arteries. Subclinical atherosclerotic disease was defined by the presence of any subclinical coronary disease or carotid plaque.

Statistical methods. Categoric and continuous variables were compared across race/ethnic groups within each gender using χ^2 tests and analysis of variance, respectively. Log-transformation was used as needed to stabilize variance before comparison of the means. Log-transformed variables were back-transformed for tabular presentation, but statistical testing was performed on the log-transformed values. Distributions of ABIs within each gender and race subgroup were compared by box-plots, as defined by Tukey.[31] The novel risk factors selected here were based on a previous study of risk factors for PAD in MESA.[18] A series of linear regression

models with ABI as the dependent variable examined the gender and race associations with ABI within the group free of major PAD risk factors and normal ABI of 1.00 to 1.30. Each model adjusted for progressively more potential confounders. For all the tests, a $P < .05$ was considered as significant.

RESULTS

Table I presents the eight gender/ethnic subgroups of this study population. As determined by the National Cholesterol Education Program calculation of the Framingham score,[32] the average 10-year risk of CHD in this subgroup was very low, at 4.2%, despite the older age of participants. Compared with the excluded MESA participants, this population presented low levels not only of variables related to the traditional risk factors (cholesterol ratio, blood pressure, blood glucose) but also of other potential risk factors (data not shown). This population also presented with a lower prevalence of subclinical atherosclerotic disease, which was uniformly distributed within the ABI range (data not shown). The Figure displays the ABI distribution across the eight sex and ethnic groups. Higher ABI values were noted in men vs women. Overall, ABI values were lower in blacks than other ethnic groups.

In a first linear regression (model 1) including age, female gender, and ethnicity, the age and gender were negatively correlated with the ABI (Table II). Compared with NHWs, being black or Chinese was significantly associated with lower ABI values. There was no evidence of interactions between these variables; that is, the association of female gender with lower ABI did not differ by age or ethnicity, nor did the association of ethnicity with ABI differ by age or gender.

In the second regression (model 2), demographic variables, and traditional and novel CVD risk factors as well as the presence or absence of subclinical atherosclerotic disease were added to model 1. Despite a comprehensive inclusion of all potential confounders, the association of female gender with lower ABI in this normal range, although attenuated, remained significant, whereas the significantly lower ABI in blacks compared with NHWs was essentially unchanged. The association of Chinese ethnicity with lower ABI was weakened after adjustment and became nonsignificant.

In addition, a high level of education and weight were positively correlated with ABI, whereas triglycerides, pack-years (in former smokers), and pulse pressure were negatively correlated. Notably, height did not show any significant correlation with PAD in this fully adjusted model; it was significantly correlated with ABI when adjusted only for age, ethnicity, and gender (data not shown).

Of interest was that none of the novel risk factors associated with PAD in the whole MESA population[18] showed any significant correlation with ABI in this healthy group. Similar results were found when the analysis was focused on a subgroup of 945 participants without any subclinical atherosclerosis (data not shown).

To estimate the effect in the MESA population, we compared the standard PAD definition of an ABI <0.90 with a gender/ethnic specific use of threshold, taking the group of NHW men arbitrarily as reference (with the 0.90 cutpoint) and calculating the other thresholds (ie, 0.88 in NHW women) in the other groups according to fully adjusted differences obtained in Table II. The prevalence of PAD in NHW women would decrease from 3.5% with the standard cutpoint to 2.2% when the specific threshold was used, and the women/men ratio in NHWs would invert from 1.25 to 0.79. Similarly, the prevalence of PAD in black women would decrease from 6.4% to 4.1%, with a women/men ratio in blacks changing from 1.05 to 0.75. Regarding ethnic disparities, the ratio for black/NHW men at 2.17 with standard definition would decrease to 1.96. In other terms, compared with NHW men, the standard PAD definition would overestimate PAD prevalence in NHW women by 37%, black men by 10%, and black women by 36%.

DISCUSSION

In this cross-sectional study focused on a subgroup of the MESA population without PAD or major risk factors, we found that even after extensive covariate adjustment, ABI varied across genders and ethnic groups, being higher in men than women, and higher NHWs than in blacks.

Peripheral arterial disease definition in epidemiologic studies. In most epidemiologic studies, an ABI <0.90 is used as a single criterion to define PAD.[3,5,10,12-15,21,33] This cutpoint is generally accepted on the basis of a clinical study comparing ABI <0.90 with arteriography, with a 90% sensitivity and 95% specificity to detect >50% arterial stenosis.[34] Correcting this for verification bias, Lijmer et al[35] reported a sensitivity of 79% and specificity of 96%. These results were obtained in clinical samples, however, and the actual diagnostic value of this threshold in the general population including different ethnic groups is unclear. In the San Diego Population Study,[16] 33 (19.6%) of 168 legs with PAD presented a normal ABI (ie, >0.90), and the disease was detected by abnormal posterior tibial artery Doppler waveforms.

This is to emphasize that the use of ABI <0.90 as the sole criteria for PAD does not exclude false negatives. In addition, even when ABI is assessed in a clinical population vs arteriography, in infrequent but not negligible cases, an ABI <0.90 leads falsely to consider a subject with normal (or <50% stenosis) angiography as having PAD.

Ankle-brachial index in healthy subjects. Paradoxically, the normal values of ABI in healthy participants are poorly studied. In subjects without any peripheral arterial stenosis, the ABI is >1.00 and <1.30. The physiologic increase in ankle systolic pressures compared with brachial arterial pressures is related to the pulse amplitude increase as a pulse travels from the aorta toward the periphery. The increase is proportional to the

Table I. Description of the Multi-Ethnic Study of Atherosclerosis population subset without evidence of peripheral arterial disease (n = 1775)

	Men					*Women*				
	NHW (n = 318)	*Blacks (n = 150)*	*Hispanics (n = 159)*	*Chinese (n = 121)*	P	*NHW (n = 453)*	*Blacks (n = 187)*	*Hispanics (n=226)*	*Chinese (n=161)*	P
Age (yrs)	60.2 (9.8)	58.4 (9.8)	59.2 (10.3)	59.1 (10.4)	.29	59.3 (9.9)	57.3 (8.9)	56.9 (9.6)	57.9 (9.6)	.006
Weight (kg)	84.2 (14.0)	88.2 (14.6)	79.9 (13.1)	65.2 (9.7)	<.001	69.7 (13.9)	80.0 (16.5)	70.4 (13.4)	56.9 (8.5)	<.001
Height (cm)	177.0 (7.2)	177.1 (6.2)	169.5 (6.0)	168.5 (6.5)	<.001	163.5 (6.3)	162.9 (7.0)	156.2 (6.1)	156.4 (5.6)	<.001
Former smoker	157 (49.7)	70 (47.6)	78 (49.4)	41 (33.9)	.022	205 (45.6)	61 (32.6)	53 (23.6)	1 (0.6)	<.001
Pack-years	12.1 (21.0)	8.3 (14.6)	10.0 (20.9)	4.8 (12.3)	.003	7.4 (13.6)	4.7 (11.4)	1.9 (8.6)	0.0 (0.1)	<.001
Blood glucose* (g/L)	0.95 (0.09)	0.96 (0.10)	0.97 (0.09)	0.98 (0.09)	.003	0.90 (0.09)	0.92 (0.10)	1.08 (0.37)	0.95 (0.08)	<.001
Total/HDL-C	3.9 (0.7)	3.6 (0.8)	4.0 (0.7)	3.7 (0.8)	<.001	3.4 (0.8)	3.3 (0.8)	3.7 (0.7)	3.6 (0.7)	<.001
Triglycerides* (g/L)	0.98 (0.43)	0.83 (0.35)	1.19 (0.62)	1.06 (0.58)	<.001	1.07 (0.52)	0.80 (0.33)	1.22 (0.58)	1.20 (0.59)	<.001
SBP (mm Hg)	115.5 (11.7)	118.1 (12.2)	116.3 (11.5)	113.3 (12.5)	<.01	111.0 (13.8)	117.5 (12.1)	112.3 (13.1)	111.1 (14.2)	<.001
DBP (mm Hg)	71.4 (8.1)	74.2 (7.3)	72.4 (7.0)	71.6 (7.9)	.003	63.8 (8.0)	69.9 (7.8)	68.4 (9.6)	65.7 (8.5)	<.001
MBP (mm Hg)	86.1 (8.5)	88.8 (8.1)	87.0 (7.4)	85.5 (8.7)	.003	79.5 (8.7)	85.8 (8.1)	80.8 (8.9)	80.8 (9.2)	<.001
PP (mm Hg)	44.1 (9.1)	43.9 (9.5)	44.0 (9.8)	41.7 (8.6)	.08	47.2 (11.8)	47.6 (10.2)	47.2 (10.7)	45.4 (11.6)	.25
Heart rate (bpm)	59.7 (8.8)	59.9 (9.3)	61.3 (8.9)	62.1 (7.7)	.027	62.9 (8.1)	63.0 (8.0)	63.2 (8.1)	64.0 (8.3)	.56
Education										
<High school	3 (1.0)	12 (8.1)	62 (39.0)	16 (13.2)		14 (3.1)	10 (5.4)	88 (38.9)	43 (26.7)	
High school	92 (29.2)	71 (48.0)	66 (41.5)	37 (30.6)	<.001	183 (40.5)	96 (51.3)	115 (50.9)	70 (43.5)	<.001
College degree	88 (27.9)	31 (20.9)	18 (11.3)	35 (28.9)		125 (27.7)	41 (21.9)	12 (5.3)	35 (21.7)	
Graduate school	132 (41.9)	34 (23.0)	13 (8.2)	33 (27.3)		130 (28.8)	40 (21.4)	11 (4.9)	13 (8.1)	
Total house income										
<$25k	17 (5.5)	22 (15.6)	61 (38.6)	55 (45.5)		58 (13.0)	38 (21.1)	108 (49.1)	73 (45.9)	
$25k-$49k	68 (22.1)	36 (25.5)	56 (35.4)	26 (21.5)	<.001	129 (29.0)	56 (31.1)	74 (33.6)	35 (22.0)	<.001
$50k-$99k	108 (35.1)	62 (44.0)	35 (22.2)	22 (18.2)		149 (33.5)	63 (35.0)	35 (15.9)	33 (20.7)	
$100k+	115 (37.3)	21 (14.9)	6 (3.8)	18 (14.9)		109 (24.5)	23 (12.8)	3 (1.4)	18 (11.3)	
CRP* (mg/L)	1.8 (3.4)	2.5 (4.3)	2.6 (3.9)	1.7 (8.9)	<.001	3.7 (6.2)	4.8 (8.0)	4.8 (6.0)	1.5 (2.9)	<.001
IL-6* (mg/L)	1.2 (1.2)	1.3 (1.0)	1.5 (1.2)	1.0 (1.0)	<.001	1.2 (1.0)	1.4 (0.9)	1.5 (1.0)	0.9 (0.7)	<.001
Fibrinogen (mg/mL)	3.1 (0.6)	3.1 (0.6)	3.3 (0.7)	2.9 (0.5)	<.001	3.3 (0.7)	3.6 (0.8)	3.6 (0.7)	3.3 (0.5)	<.001
PAP* (nM)	4.3 (1.5)	4.7 (1.7)	4.3 (1.7)	4.0 (1.5)	.002	5.1 (2.0)	5.3 (2.0)	4.8 (2.1)	4.0 (1.4)	<.001
D-dimers* (μg/mL)	0.2 (0.2)	0.3 (0.4)	0.3 (0.4)	0.3 (0.8)	.12	0.3 (0.4)	0.4 (0.7)	0.4 (1.4)	0.2 (0.3)	<.001
Homocysteine* (μmol/L)	9.6 (3.1)	10.2 (4.5)	9.3 (2.2)	9.0 (1.9)	.01	8.2 (5.6)	8.1 (2.2)	7.6 (2.6)	7.4 (1.8)	.001
CAC >0	174 (54.7)	45 (30.0)	70 (44.0)	49 (40.5)	<.001	119 (26.3)	32 (17.1)	36 (15.9)	43 (26.7)	.003
Carotid lesions	105 (33.4)	29 (19.9)	50 (32.1)	16 (13.3)	<.001	134 (30.3)	43 (23.6)	38 (17.4)	26 (16.2)	<.001
ABI	1.16 (0.06)	1.14 (0.07)	1.16 (0.06)	1.14 (0.06)	.003	1.13 (0.07)	1.11 (0.06)	1.12 (0.06)	1.11 (0.06)	.003

NHW, Non-Hispanic whites; *HDL-C*, High-density lipoprotein cholesterol; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *MBP*, mean blood pressure; *PP*, pulse pressure; *CRP*, C-reactive protein; *IL*, interleukin; *PAP*, plasmin-antiplasmin complex; *CAC*, coronary artery calcification; *ABI*, ankle-brachial index.

Numbers are mean (standard deviation) for continuous variables or n (%) for categoric variables.

*Indicates that significance was tested on natural log transformed scale.

Table II. Correlates of ankle-brachial index in healthy subjects (linear regression models)

	Model 1 coefficient (95% CI)	*Model 2 coefficient (95% CI)*
Age (10 years)	−0.008 (−0.01, −0.005)	−0.002 (−0.007, 0.002)
Female gender	−0.036 (−0.042, −0.030)	−0.017† (−0.027, −0.006)
Ethnicity		
Non-Hispanic white	Ref	Ref
Black	−0.017 (−0.026, −0.009)	−0.019‡ (−0.029, −0.010)
Hispanic	−0.002 (−0.010, 0.006)	0.008 (−0.002, 0.019)
Chinese	−0.020 (−0.028, −0.011)	−0.007 (−0.019, 0.004)
Weight (per kg)	—	0.0006‡ (0.0003, 0.0009)
Height (per cm)	—	0.0003 (−0.0003, 0.0009)
Ever smoking	—	0.004 (−0.004, 0.012)
Pack-years (per unit)	—	−0.0004† (−0.0006, −0.0001)
Glucose* (g/L)	—	0.0347 (−0.0007, 0.0701)
Total/HDL-C	—	0.0044 (−0.0006, 0.0094)
Triglycerides* (g/L)	—	−0.0102* (−0.0186, 0.0017)
MBP (per mm Hg)	—	−0.0001 (−0.0005, 0.0003)
PP (per mm Hg)	—	−0.0005† (−0.0009, −0.0001)
Heart rate (per bpm)	—	−0.0004 (−0.0008, 0.0001)
Education		
<High school		Ref
Completed high school	—	0.006 (−0.004, 0.017)
College		0.008 (−0.005, 0.020)
Graduate school		0.021† (0.008, 0.033)
Income		
<$25k		Ref
$25k-$49k	—	0.001 (−0.008, 0.009)
$50k-$99k		−0.002 (−0.012, 0.007)
$100k+		−0.004 (−0.015, 0.008)
Hs-CRP* (mg/L)	—	−0.0022 (−0.0058, 0.0014)
IL-6* (mg/L)	—	−0.0003 (−0.0060, 0.0055)
Fibrinogen (per mg/mL)	—	−0.0000 (−0.0001, 0.0001)
PAP* (nM)	—	−0.0006 (−0.0111, 0.0098)
D-dimers* (μg/mL)	—	−0.0006 (−0.0046, 0.0034)
Homocysteine* (μmol/L)	—	0.0098 (−0.0028, 0.0222)
CAC >0	—	−0.003 (−0.011, 0.004)
Carotid lesions	—	−0.001 (−0.008, 0.007)

HDL-C, High-density lipoprotein cholesterol; *MBP,* mean blood pressure; *PP,* pulse pressure; *hs-CRP,* high-sensitive C-reactive protein; *IL,* interleukin; *PAP,* plasmin-antiplasmin complex; *CAC,* coronary artery calcification.
*$P < .05$.
†$P < .01$.
‡$P < .001$.
*Units that are natural log-transformed.

distance from the heart, resulting in a higher SBP in ankle than brachial arteries.[36]

Gender differences in ankle-brachial index. In an ancillary study from the San Luis Valley Diabetes Study, Hiatt et al[23] analyzed the ABI distribution in a subgroup of nonsmokers without glucose intolerance, blood pressure >140/90 mm Hg, or any CVD history. This subgroup presented 2.5th percentile values at 0.91 for women and 0.98 for men. It has been suggested that the lower ABI among women is related to a lower height,[33] leading to a lesser pulse amplification; however, after adjustments for age, sex, arm pressure, and diabetes status, the contribution of height to ABI turned to be modest, about 1 mm Hg ankle pressure increase for each 10 cm in height.[23] In a population without clinical CVD, London et al[37] reported a positive correlation between body height and ABI, but women showed a lower ABI even after adjustments for age and height.

We initially found a significant correlation between height and ABI adjusted for age, gender, and ethnicity, but we did not find height as an independent significant determinant of ABI in healthy participants in the fully adjusted model. The adjusted contribution of height to ABI seems negligible. According to its partial coefficient, ABI was an average of 0.003 units higher for every 10 cm more height.

Our data suggest that the ABI is about 0.02 lower in women than men. Consequently, a unisex ABI threshold used for PAD definition might partially explain higher rates of PAD in women.[11,13,21] This is consistent with data from the San Diego Population Study,[16] a population study where the PAD definition included an ABI <0.90 as well as other criteria (abnormal Doppler waveforms and revascularization history). In this population, a lower ABI was reported for women (1.12 vs 1.16 for men). This suggests a shift to lower ABI values for

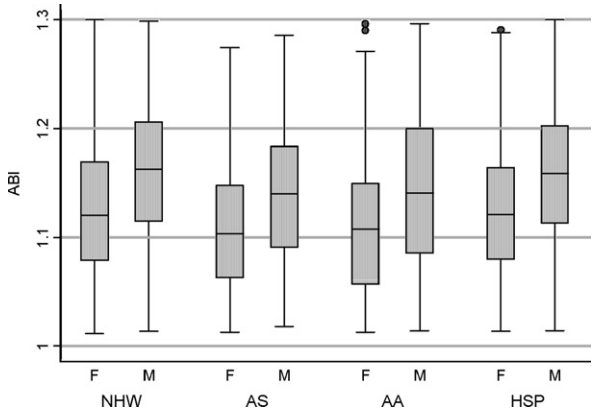

Fig. Box plot of ankle-brachial index *(ABI)* by gender and race/ethnicity in participants without peripheral arterial disease or risk factors. Bullets correspond to individual cases beyond the standard deviation. Data are presented with standard deviation. *NHW,* Non-Hispanic whites; *AS,* Chinese; *AA*, blacks; *HSP,* Hispanics.

women compared with men and might result in a higher rate of low (<0.90) ABI values in women. When PAD was defined by several criteria, however, higher rates of PAD were reported in men.[16] In the National Health and Nutrition Examination Survey (NHANES)[13] and Atherosclerosis Risk in Communities (ARIC)[21] reports, the prevalence of ABI <0.90 in women aged 40 to 59 years was intriguingly estimated to be about twice as high as in men. In the ARIC study,[21] in contrast to higher prevalence of PAD in women when ABI thresholds were fixed at 0.95 or 0.90, men had higher rates of PAD when lower thresholds were used (0.85 or 0.80).

Ethnic differences in peripheral arterial disease rates. In clinical series, PAD in blacks is reported as more frequent,[38] more severe,[39,40] and with poorer outcome.[39,41-45] Nonetheless, the higher prevalence of diabetes[11,21,46] and hypertension[11,21,47] in blacks, as well as social disparities (eg, different accessibility to medical care), may contribute to outcome. Furthermore, this higher rate of PAD does not adequately match with a higher rate of clinical symptoms. In a study[48] mixing one community-dwelling population and two vascular laboratory populations, the most severe pain categories (eg, typical intermittent claudication) were significantly less common in blacks. Recent data also showed no increased rates of functional decline in blacks vs whites with PAD.[49] Two conclusions can be made:

First, black subjects could present clinical symptoms in a more progressed stage of the disease. This is plausible since PAD affects more distal arteries[50] in blacks, and the rates of diabetes and neuropathy are higher in this ethnic group.[10,40] This could result in delayed medical care and worse prognosis. Alternatively, but not exclusively, this could also indicate that a similar low level of ABI does not reflect an equivalent extent of the disease in whites and in blacks. The latter explanation is concordant with our findings that even in healthy subjects, ABI is lower in blacks compared with whites.

Similarly, population-based studies report higher rates of PAD in blacks, even after adjustments for traditional and novel risk factors as well as socioeconomic status.[10,13,16,18,20,21] The San Diego population study[16] excluded a greater susceptibility of blacks to PAD risk factors, after testing interaction terms between ethnicity and nine major risk factors. It is of interest that when different ABI thresholds were used in the ARIC study,[21] from 0.80 to 0.95, the ratio of black/NHW males of age-adjusted PAD prevalence decreased from 2.2 to 1.2. This may suggest that PAD in blacks is more severe, or this could partly be due to the different distribution of ABI in ethnic groups, as observed here. The approximately 0.02 difference between NHWs and blacks in our study is similar to that observed after adjustment for age, gender, and height in the ARIC study.[21]

Regarding the other ethnic groups, the NHANES reported[10,13] a trend to a higher adjusted-rate of PAD in Mexican Americans. In MESA[18], adjusted for age, gender, education, income, and traditional risk factors, the prevalence of an ABI ≤0.90 was significantly lower in Chinese Americans and Hispanics. We found a different ABI distribution in healthy Chinese and Hispanics vs NHW (Fig), but this difference was strongly attenuated by adjustments. We conclude that unlike our findings in blacks, differences observed in *healthy* Chinese and Hispanic subjects are mainly related to different distributions of risk factors.

Biologic explanations. The basic difference on ABI values in different gender/ethnic groups without PAD must be related to other conditions than atherosclerosis. The pressure amplification from the central to peripheral arteries depends on the arterial geometry and elasticity variations between the aorta and the site of measurement.[36] Aortic stiffening causes premature return of the pulse wave reflection from the periphery, which diminishes until eliminating the normal augmentation of the pressure waveform from central to peripheral arteries,[28] such as the brachial artery, and even more to ankle arteries, leading to an ABI reduction. The ABI, consequently, is affected both by the presence of any (atherosclerotic) obstruction and by the aortic and peripheral stiffness.

Using magnetic resonance imaging in a subset of the MESA population, a thicker thoracic aorta was reported among blacks.[51] In middle age, the aorta in blacks is stiffer than in whites.[52] This is due to a higher aortic collagen concentration.[53] Notably, this effect is visible in our study, as pulse pressure, an indirect marker of large-vessels stiffness,[54] was inversely correlated with ABI. This was also reported in the Cardiovascular Health Study.[55] Even though aortic stiffening is of major prognostic importance,[56] this is a different pathology from PAD.

Other correlates of normal ankle-brachial index. Among other significant contributors to ABI determina-

tion in this study, a high level of education was consistently correlated with a higher ABI. Similarly, a higher education level is protective for PAD in the entire MESA population.[18] Despite a similar trend, this was not confirmed in the San Diego Population Study,[16] but it could be related to the concomitant inclusion of the type of occupation in that predictive model, a variable that we did not test. Education may index other behavioral and socioeconomic factors not assessed in this study.

Study implications. The residual effect of gender and ethnicity in our fully adjusted model could at the first glance be considered as negligible. At an individual scale, a 0.02 ABI difference between men and women or whites and blacks is quite below the ABI measurement variability.[56,57] Henceforth, the single 0.90 ABI threshold for the diagnosis of PAD remains valid in the clinical setting, even though our data could be useful in some borderline ABI values, especially in black women.

At a population level, however, a small change in ABI threshold affects substantially the estimates of disease burden. The women/men ratios in blacks and whites inverted <1 when gender/ethnic specific thresholds were used vs the unique <0.90 cutpoint. Similarly, the prevalence of PAD in blacks, especially in women, would substantially be lower with this new approach, and the disparities with whites, although remaining consistent, would be reduced at some extent.

Study limitations. Among other potential correlates, lipoprotein (a) was not available in this study. Furthermore, hormonal and genetic data were not studied. We cannot exclude their role (or that of other unknown risk factors) as confounding factors in these analyses. It seems unlikely, however, that the addition of one or more additional covariates would remove the gender and ethnic differences observed given the extensive adjustment we have already incorporated. In addition, we did not find any correlation in this healthy population between ABI and subclinical atherosclerosis in other territories. This reduces the risk of missing unknown risk factors of atherosclerosis that could explain gender/ethnic disparities on normal ABI values.

CONCLUSION

To our knowledge, this is the first multiethnic study to assess the contribution of gender and ethnicity to the determination of ABI in low-risk subjects with no evidence of PAD. Our main results confirm the hypothesis that even after extensive control of confounders, gender and ethnicity remain independently associated with ABI. This suggests that some inherent physiologic (eg, hormonal, genetic) differences in ABI normal levels exist between different gender/ethnic groups. We consider that such differences, although small in magnitude, are highly statistically significant and can distort population estimates of disease burden.

AUTHOR CONTRIBUTIONS

Conception and design: VA, MC, MA
Analysis and interpretation: VA, MC, RM, MA, MM, DG, TM
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Writing the article: VA, MC, RM, MA, MM, DG, TM
Critical revision of the article: VA, MC, RM, MA, MM, DG, TM
Final approval of the article: VA, MC, RM, MA, MM, DG, TM
Statistical analysis: RM
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