

Predictors of Carotid Thickness and Plaque Progression During a Decade

The Multi-Ethnic Study of Atherosclerosis

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Background and Purpose—Carotid artery intima-media thickness (IMT) and plaque are noninvasive markers of subclinical arterial injury that predict incident cardiovascular disease. We evaluated predictors of longitudinal changes in IMT and new plaque during a decade in a longitudinal multiethnic cohort.

Methods—Carotid IMT and plaque were evaluated in Multi-Ethnic Study of Atherosclerosis (MESA) participants at exams 1 and 5, a mean (standard deviation) of 9.4 (0.5) years later. Far wall carotid IMT was measured in both common and internal carotid arteries. A plaque score was calculated from all carotid segments. Mixed-effects longitudinal and multivariate regression models evaluated associations of baseline risk factors and time-updated medication use with IMT progression and plaque formation.

Results—The 3441 MESA participants were aged 60.3 (9.4) years (53% women; 26% blacks, 22% Hispanic, 13% Chinese); 1620 (47%) had carotid plaque. Mean common carotid artery IMT progression was 11.8 (12.8) $\mu\text{m}/\text{year}$, and 1923 (56%) subjects developed new plaque. IMT progressed more slowly in Chinese ($\beta=-2.89$; $P=0.001$) and Hispanic participants ($\beta=-1.81$; $P=0.02$), and with higher baseline high-density lipoprotein cholesterol (per 5 mg/dL; $\beta=-0.22$; $P=0.03$), antihypertensive use ($\beta=-2.06$; $P=0.0004$), and time on antihypertensive medications (years; $\beta=-0.29$; $P<0.0001$). Traditional risk factors were associated with new plaque formation, with strong associations for cigarette use (odds ratio, 2.31; $P<0.0001$) and protection by black ethnicity (odds ratio, 0.68; $P<0.0001$).

Conclusions—In a large, multiethnic cohort with a decade of follow-up, ethnicity was a strong, independent predictor of carotid IMT and plaque progression. Antihypertensive medication use was associated with less subclinical disease progression. (*Stroke*. 2014;45:3257-3262.)

Key Words: atherosclerosis ■ carotid arteries ■ epidemiology ■ risk factors

Carotid artery intima-media thickness (IMT) and plaque presence are noninvasive markers of subclinical arterial injury that predict incident cardiovascular disease (CVD).¹⁻³ Although clinical trials have used short-term change in carotid IMT as a surrogate end point to assess the impact of pharmacotherapeutic agents in homogenous populations with high levels of CVD risk factors, little is known about the predictors of carotid IMT progression in large, heterogeneous populations.⁴ Carotid plaque represents a later stage of arterial injury. Its presence and extent also are associated with incident CVD, yet little is known about the predictors of carotid plaque progression.^{1,5-8} The predictors of carotid IMT and plaque progression in an ethnically diverse population are unknown. We

hypothesized that CVD risk factors are the major predictors of longitudinal changes in carotid IMT and plaque progression, but that race/ethnicity and use of antihypertensive and lipid-lowering medications also would affect progression.

Methods

Participants

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort of 6814 participants free of known CVD at baseline. The aim of MESA is to investigate risk factors and subclinical CVD progression in an ethnically diverse population.⁹ MESA enrolled participants from 6 different field centers located in Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota.

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Details of MESA's design have been published previously.⁹ The study was approved by the institutional review boards of all MESA field centers, the University of Washington Data Coordinating Center, and the University of Wisconsin Atherosclerosis Imaging Research Program. All participants provided informed consent. Our analysis was restricted to those participants with both baseline (examination 1; July 2000 to August 2002) and follow-up (examination 5; March 2010 to February 2012) risk factor and carotid ultrasound data. Baseline laboratory samples were collected after a 12-hour fast.

Carotid Ultrasonography

At baseline, B-mode ultrasound images of the right and left common, bifurcation, and internal carotid artery (ICA) segments were recorded on Super-VHS videotape with a Logiq 700 ultrasound system using the M12L transducer (General Electric Medical Systems; common carotid artery [CCA] frequency, 13 MHz). Video images were digitized at high resolution and frame rates using a Medical Digital Recording device (PACSGEAR, Pleasanton, CA) and converted into DICOM-compatible digital records. The same ultrasound system and digitizing equipment were used at examination 5; however, the video output was directly digitized using the same recorder settings without videotape. Trained, certified sonographers used preselected reference images from examination 1 to match the scanning conditions of the initial study, including display depth, angle of approach, internal landmarks, degree of jugular venous distension, and ultrasound system settings. Ultrasound images were reviewed and interpreted by the University of Wisconsin Atherosclerosis Imaging Research Program MESA Carotid Ultrasound Reading Center. Images were imported into syngo Ultrasound Workplace reading stations loaded with Arterial Health Package software (Siemens Medical, Malvern, PA) for IMT measurement and plaque scoring. Measurements of examination 1 and examination 5 carotid ultrasound images were performed simultaneously. Images were matched side by side on a video monitor and measured contemporaneously; however, examination 1 IMT measurements were not considered in choosing the examination 5 site or making the examination 5 measurements.

This analysis primarily focused on CCA IMT and carotid plaque score. Internal carotid artery IMT data are presented in the online-only Data Supplements I and II. The distal CCA was defined as the distal 10 mm of the vessel. IMT was defined as the IMT measured as the mean of the mean left and right mean far wall distal CCA wall thicknesses. Carotid plaque score (0–12) was defined as the number of carotid plaques in the internal, bifurcation, and common segments of both carotid arteries.¹⁰ Carotid plaque was defined as a discrete, focal wall thickening ≥ 1.5 cm or focal thickening $\leq 50\%$ greater than the surrounding IMT.¹

Ultrasound Quality Assurance

The intraclass correlation coefficient for intrareader reproducibility for mean CCA IMT was 0.99. The intraclass correlation coefficient for inter-reader CCA IMT reproducibility was 0.95. For mean ICA, intrareader reproducibility was between 0.98 and 0.99 and inter-reader reproducibility was 0.93. To assess scan–rescan reproducibility, 44 scans were repeated by 3 sonographers. The Pearson correlation coefficient was 0.94. Mean (SD) differences were 0.006 (0.036–0.760) mm. There were no outliers noted on limit of agreement analysis for matched segments. For carotid plaque presence and score, intrareader reproducibility was $\kappa=0.83$ (95% confidence interval, 0.70–0.96) and inter-reader reproducibility was $\kappa=0.89$ (95% confidence interval, 0.72–1.00).

Statistical Methods

Descriptive statistics are reported as means (SDs) for continuous and percentages for categorical variables. Paired *t* tests were used to compare examination 1 and 5 continuous variables; χ^2 tests for categorical variables. Plaque score progression by ethnicity was compared using a Kruskal–Wallis test.

For IMT progression, 2 sets of complimentary models were created. First, a multivariate linear regression model with scaled change

of carotid IMT (micrometers per year) as the outcome measure was created. Scaled change accounted for variability in participant follow-up times. Second, a mixed-effects longitudinal change model with adjustment for estimated baseline with the outcome modeled as a continuous variable (micrometers) was created (online-only Data Supplement III).¹¹ This model was fit with random slopes and intercepts for each participant and contained 3 components: cross-sectional, longitudinal, and transient.¹¹ The cross-sectional component analyzed the association of baseline CVD risk factors with estimated carotid IMT at baseline, whereas the longitudinal component analyzed this association with IMT progression (micrometers per year) during the observation period. When modeling associations

Table 1. Baseline and Follow-Up Descriptive Statistics

Variable	Examination 1 (n=3441)	Examination 5 (n=3441)	P Value
Age, y	60.3 (9.4)	69.8 (9.3)	<0.0001
Male sex, % (n)	47.0% (1618)		
Race/ethnicity, % (n)			
White	39.2% (1350)		
Black	26.4% (909)		
Hispanic	21.5% (740)		
Chinese	12.9% (442)		
Annual income, % (n)			
<\$16 000	14.6 (490)	15.3 (509)	<0.0001
\$16 000–\$34 999	24.2 (812)	25.0 (831)	
\$35 000–\$99 999	45.1 (1509)	42.1 (1398)	
\geq \$100 000	16.0 (537)	17.6 (586)	
Smoking, % (n)			
Current	11.4% (390)	7.31% (250)	<0.0001
Former	36.6% (1258)	47.1% (1610)	
Never	52.0% (1788)	45.7% (1562)	
Systolic blood pressure, mm Hg	124.4 (20.2)	124.3 (20.8)	0.73
High-density lipoprotein cholesterol, mg/dL	51.01 (14.9)	55.93 (16.9)	<0.0001
Total cholesterol, mg/dL	194.1 (35.1)	182.7 (36.9)	<0.0001
Glucose, mg/dL	95.1 (26.0)	102.1 (27.8)	<0.0001
Body mass index, kg/m ²	28.3 (5.3)	28.5 (5.5)	<0.0001
Diabetes mellitus, % (n)	10 (345)	19.7 (674)	<0.0001
Family history of coronary heart disease, % (n)	43.5 (1415)	N/A	N/A
Use of antihypertensive medication, % (n)	34.9 (1200)	55.8 (1919)	<0.0001
Use of statin medication, % (n)	15.1 (519)	37.4 (1287)	<0.0001
Mean–mean CCA IMT, μ m	754.6 (179.8)	865.5 (198.2)	<0.0001
Left CCA IMT, μ m	756.4 (210.4)	866.1 (233.8)	<0.0001
Right CCA IMT, μ m	753.6 (190.2)	866.5 (215.2)	<0.0001
Left CCA IMT absolute progression, μ m	109 (160.2)		0.17*
Right CCA IMT absolute progression, μ m	114.2 (141.8)		
Carotid plaque presence, % (n)	47.1% (1620)	68.0% (2338)	<0.0001
Carotid plaque score	1.11 (1.64)	2.29 (2.45)	<0.0001

Values are mean (SD) unless noted otherwise. CCA indicates common carotid artery; IMT, intima-media thickness; and N/A, not available.

*P value represents the comparison between left CCA and right CCA absolute progression.

of change, inclusion of the measured baseline as a covariate can result in measurement error, so measured baseline IMT was not included as a covariate in either model to avoid bias.¹² In the mixed-effects model, baseline IMT was accounted by the cross-sectional term to estimate the baseline IMT using both fixed and random effects. The mixed-effects model permits improved statistical efficiency given subject-specific random effects and maximum use of available data even among those with missing data. To demonstrate the consistency between the 2 models, both sets of results are shown.

For new carotid plaque formation, a multivariate logistic regression model was created. Because we desired to construct the most informative model, all models for carotid IMT progression and plaque formation included the covariates listed in the online-only Data Supplement IV and also included baseline antihypertensive and statin pharmacotherapy or their time-varying use (years). Statistical significance was set at 2-sided $P < 0.05$. Analyses were performed in SAS (version 9.2, SAS Institute Inc, Cary, NC).

Results

Descriptive Characteristics

Participants were followed for a mean (SD) of 9.4 (0.5) years. Their characteristics are described in Table 1.

Carotid IMT Progression: Multivariate Model of Scaled Change

At examination 1, several traditional CVD risk factors were associated with CCA IMT (Table 2). Predictors of IMT progression were similar in models using baseline antihypertensive and statin pharmacotherapy and time-varying use of these medications (Tables 3 and 4). Diabetes mellitus ($\beta = 2.85$; $P = 0.02$) and time on statin pharmacotherapy ($\beta = -0.16$; $P = 0.04$) were additional predictors of IMT progression in the time-varying model. In both models, antihypertensive medication use was associated with slower IMT progression ($P < 0.0001$) as were Chinese ($P = 0.001$) and Hispanic ethnicities ($P = 0.02$) (Figure). Predictors of ICA IMT progression were similar to CCA IMT progression (online-only Data Supplements I and II).

Carotid IMT Progression: Mixed-Effects Longitudinal Model

Similar to the multivariate models, in the cross-sectional component of the mixed-effects model, traditional CVD risk factors were associated with estimated baseline CCA IMT (Table 2). The estimated CCA IMT baseline in the mixed-effects model yielded the same risk factor associations with similar parameter estimates when compared with a cross-sectional analysis using a multivariate linear model and examination 1 IMT. Also, predictors of IMT progression were similar between models using baseline antihypertensive and statin pharmacotherapy, as well as time-varying use of these medications (Tables 3 and 4). The only slight difference was that baseline statin use was a statistically significant predictor in the mixed-effects model ($\beta = 1.59$; $P = 0.03$; Table 3). Antihypertensive medication use was strongly associated with slower IMT progression modeled as either baseline ($P = 0.0004$) or time-varying ($P = 0.005$) use as was Chinese ethnicity ($P = 0.01$).

Carotid Plaque Formation

There were 1923 (56%) participants that formed new carotid plaque. Several traditional CVD risk factors were associated with carotid plaque formation. Whites had higher plaque score. More than 59% of whites formed new plaque; Chinese had the lowest new plaque formation rate (49.8%; online-only Data Supplement V). There only were slight differences between the baseline antihypertensive and statin pharmacotherapy models (online-only Data Supplement VI) and the time-varying models (Table 5). Current cigarette smoking was a strong predictor of new plaque formation (odds ratio, 2.31; $P < 0.0001$). Compared with white ethnicity, black, Hispanic, and Chinese ethnicities were associated with less plaque formation.

Discussion

In this large, multiethnic cohort with nearly a decade of prospective observation, Hispanic and Chinese ethnicity as well

Table 2. Baseline Traditional Risk Factors and Baseline (Examination 1) Carotid Intima-Media Thickness

Predictor	Multivariate Linear Regression Model* (Model $R^2 = 0.29$)		Mixed-Effects Longitudinal Model* (Estimated Baseline)	
	Parameter Estimate (SE)	P Value	Parameter Estimate (SE)	P Value
Age (per decade)	74.49 (3.49)	<0.0001	73.62 (3.34)	<0.0001
Male sex	39.35 (6.75)	<0.0001	39.03 (6.41)	<0.0001
Body mass index (per 5 kg/m ²)	17.45 (3.27)	<0.0001	14.59 (3.06)	<0.0001
Systolic blood pressure (per 10 mm Hg)	14.21 (1.60)	<0.0001	14.80 (1.53)	<0.0001
Fasting glucose (per 10 mg/dL)	3.54 (1.59)	0.03	3.12 (1.49)	0.04
High-density lipoprotein cholesterol (per 5 mg/dL)	-3.06 (1.14)	0.007	-3.33 (1.09)	0.002
Total cholesterol (per 10 mg/dL)	4.12 (0.86)	<0.0001	4.12 (0.82)	<0.0001
Black ethnicity	29.78 (7.80)	0.0001	28.72 (7.46)	0.0001
Current cigarette use	22.26 (9.50)	0.02	23.59 (9.17)	0.01
Former cigarette use	20.90 (6.40)	0.001	20.20 (6.13)	0.001

*Outcome modeled in micrometers.

Table 3. Predictors of Carotid Intima-Media Thickness Progression: Baseline Use of Antihypertensive and Statin Medications

Predictors	Multivariate Linear Regression Model*		Mixed-Effects Longitudinal Model*	
	Parameter Estimates (SE)	P Value	Parameter Estimates (SE)	P Value
Chinese ethnicity	-2.89 (0.88)	0.001	-2.29 (0.90)	0.01
Hispanic ethnicity	-1.81 (0.76)	0.02	-1.40 (0.79)	0.08
High-density lipoprotein cholesterol (per 5 mg/dL)	-0.22 (0.10)	0.03	-0.18 (0.10)	0.08
Antihypertensive medication use (baseline)	-2.06 (0.58)	0.0004	-2.11 (0.60)	0.0004
Statin medication use (baseline)	1.31 (0.73)	0.07 (NS)	1.59 (0.75)	0.03

NS indicates nonsignificant.

*Outcome modeled in micrometers per year.

as antihypertensive medication use at baseline and throughout the observation period consistently were associated with slower carotid IMT progression. Cigarette smoking at baseline was associated with an increase in new carotid plaque formation, whereas black ethnicity was associated with less carotid plaque formation.

Numerous clinical trials have evaluated the short-term effects of pharmacotherapeutic interventions on carotid IMT progression in homogenous populations with increased levels of a specific risk factor. However, few studies examined longitudinal IMT progression in a heterogeneous population that is more representative of US population and healthier individuals than clinical trial participants. Previous investigations have been limited by factors including low inter- and intrareader correlations (0.59–0.75), low interscan reproducibility measures, use of lower-frequency ultrasound transducers, manual IMT measurement, restriction to 1 carotid artery, and homogenous cohorts.⁶

Consistent associations between CVD risk factors and prevalent carotid IMT have been described; however, few studies investigated progression of carotid IMT and plaque. Our model of cross-sectional associations between CCA IMT and risk factors had 1 of the highest adjusted R^2 values reported to date (0.29).^{5,13–15} Despite relatively strong associations of traditional risk factors and baseline IMT, in the fully adjusted model only Chinese and Hispanic ethnicities and use

of antihypertensive medications were consistent, independent predictors of slower IMT progression. The scaled change and mixed-effects models yielded similar results with similar parameter estimates. Inter- and intrareader reliability and scan reproducibility measures were among the highest reported with precision as high as those attained in clinical trials.^{6,16,17}

In the fully adjusted model, we observed a strong, independent protective effect of Chinese and Hispanic ethnicity on IMT progression. MESA is a unique cohort, because no previous cohort has had the ethnic diversity to demonstrate ethnic associations with IMT progression.⁵ We found a persistent and strong inverse effect of antihypertensive medications on progression of subclinical carotid disease. The strong protective effect of antihypertensive medication use is consistent with current knowledge of compensatory changes to arterial walls to elevated systemic blood pressures. In clinical trials, the use of antihypertensive medications is associated with decreased IMT progression.^{18,19} Based on these data, antihypertensive medication use may be the strongest modifiable predictor of slowing IMT progression over time. In contrast with antihypertensive medication use, statin medication use at baseline was weakly and positively associated with IMT progression; however, when modeled as a time-updated covariate, time on statin medication was inversely associated with IMT progression. Statin medication use at baseline may be a marker of an

Table 4. Predictors of Carotid Intima-Media Thickness Progression With Antihypertensive and Statin Medications Modeled as Time-Varying Covariates

Predictors	Multivariate Linear Regression Model*		Mixed Effects Longitudinal Model*	
	Parameter Estimates (SE)	P Value	Parameter Estimates (SE)	P Value
Chinese ethnicity	-2.93 (0.88)	0.0009	-2.34 (0.90)	0.009
Hispanic ethnicity	-2.09 (0.76)	0.006	-1.59 (0.79)	0.04
High-density lipoprotein cholesterol (per 5 mg/dL)	-0.24 (0.10)	0.02	-0.19 (0.10)	0.06
Antihypertensive medication use, y	-0.29 (0.07)	<0.0001	-2.04 (0.72)†	0.005
Statin medication use, y	-0.16 (0.08)	0.04	-0.95 (0.74)†	0.20
Diabetes mellitus	2.85 (1.23)	0.02	1.89 (1.23)	0.13

*Outcome modeled in micrometers per year unless noted.

†Modeled in micrometers of change over observation period.

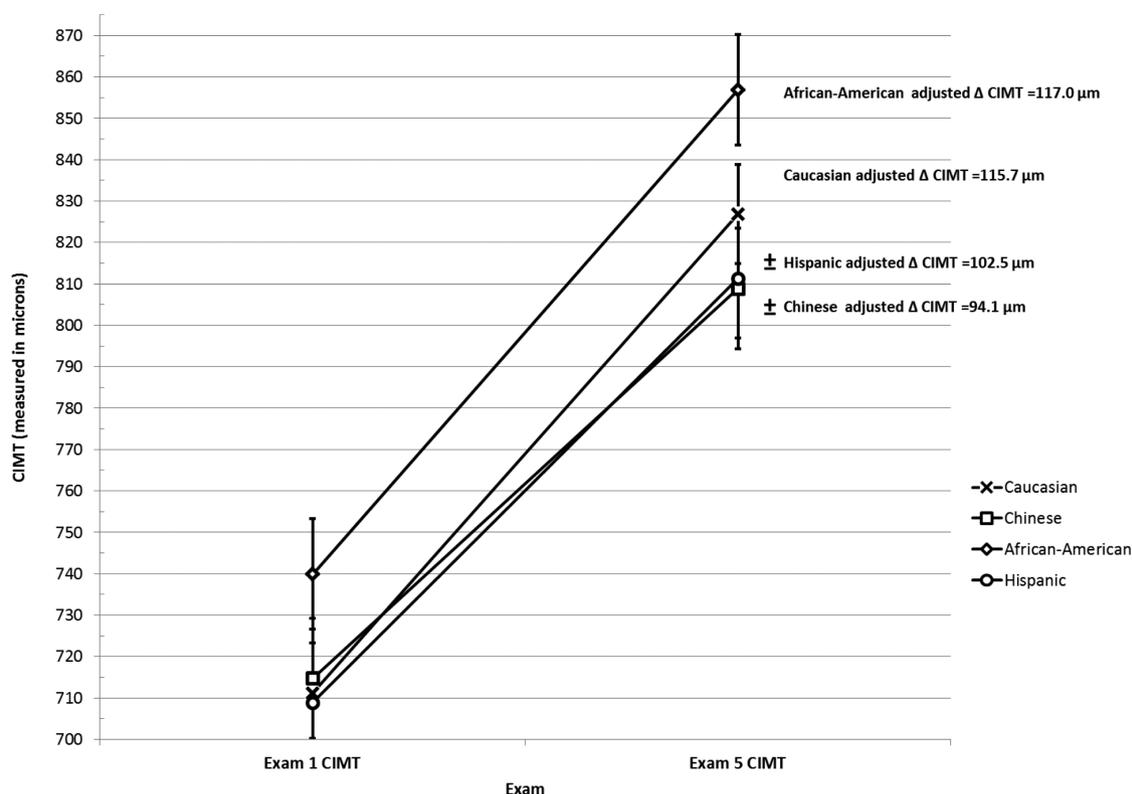


Figure. Adjusted carotid intima-media thickness (CIMT) progression by ethnicity. Error bars represent estimated means \pm SE of the mean. Models adjusted for age, sex, body mass index, systolic blood pressure, tobacco use, total cholesterol, high-density lipoprotein, glucose, income, education, family history, diabetes mellitus, antihypertensive medication use, and statin medication use. \pm Adjusted IMT progression rate differs compared with white ethnicity ($P < 0.05$).

increased antecedent burden of CVD risk factors before study enrollment. We did not find a significant effect on plaque progression and use of statin medications.

Traditional CVD risk factors are associated with carotid plaque presence and burden; however, few studies have analyzed the predictors of carotid plaque progression over time.^{20–22} In our study, current cigarette smoking was a strong predictor of new plaque across ethnicities. When risk of new plaque formation was adjusted for traditional CVD risk factors, Hispanic, blacks, and Chinese ethnicities had lower risks of new carotid plaque. These ethnic differences in carotid plaque progression are novel and clinically relevant findings because prior investigations were of whites. Our carotid plaque findings are similar to those in other arterial territories. In the coronary arteries, black ethnicity is associated with less calcification and slower calcium progression, despite more adverse risk factor profiles.^{23,24} In our study, black ethnicity was associated with thicker CCA IMT but with less carotid plaque formation than whites. Because of pathophysiological differences between arterial wall thickening and plaque formation, it is not surprising that the predictors for progression of these markers differ.

Limitations

As an observational study, the described associations do not confirm causation. Our participants were a subset of the MESA who returned for examination 5 and may be biased based on survival to this examination. Examination 5 participants were healthier and less likely to have a nonfatal CVD event than the original MESA cohort, which could have reduced the strength of the associations

we identified. Carotid IMT and plaque progression are surrogate markers for CVD risk; however, they provide important insights into the pathophysiology of arterial injury, the substrate for cerebrovascular disease and cognitive decline. Carotid artery disease also is strongly associated with and reflective of changes in other arterial beds. This investigation focused on CCA IMT. Only half as many participants had ICA images available for analysis given the inability to match ICA segments across examinations, yet the results (online-only Data Supplements I and II) were similar. Although regression models were adjusted for measured risk

Table 5. Predictors of New Carotid Plaque: Antihypertensive and Statin Medications as Time-Varying Covariates

Variable	OR (95% CI)	P Value
Age (per decade)	1.63 (1.49–1.79)	<0.0001
Current cigarettes	2.31 (1.79–2.99)	<0.0001
Total cholesterol (per 10 mg/dL)	1.03 (1.01–1.06)	0.005
Black	0.68 (0.55–0.83)	0.0002
Chinese	0.69 (0.53–0.91)	0.008
Hispanic	0.75 (0.59–0.95)	0.016
Former cigarettes	1.27 (1.08–1.51)	0.004
Systolic blood pressure (per 10 mm Hg)	1.1 (1.05–1.15)	<0.0001
Fasting glucose (per 10 mg/dL)	1.05 (1.01–1.1)	0.022
High-density lipoprotein cholesterol (per 5 mg/dL)	0.97 (0.94–1.0)	0.021

Maximum rescaled R^2 for new carotid plaque=0.15; area under the curve for new carotid plaque=0.70. CI indicates confidence interval; and OR, odds ratio.

factor and sociodemographic variables, unmeasured lifestyle exposures and risk factors that may be specific to each ethnicity cannot be accounted for. We cannot exclude a systematic error in measurement because of nonblinding; however, the random error associated with measuring such a small quantity on 1 examination would be the most prominent source of bias, rather than any systematic measurement bias. Any systematic measurement error that did occur would be nondifferential in nature and, therefore, would bias the results toward the null. Also, segments were traced with semiautomated border detection tool with minimal edits by the reader, except when interface determination by the software was incorrect. Finally, MESA is a US cohort, so the generalizability of these findings to populations outside the United States may be limited.

Conclusions

Ethnicity is associated independently with progression of carotid wall thickening and plaque formation, subclinical markers of arterial injury and CVD risk. The most powerful pharmacological and modifiable risk factors impacting progressive carotid wall injury are use of antihypertensive medications and cigarette smoking.

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