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Distribution of calcium volume, density, number, and type of coronary vessel with calcified plaque in South Asians in the US and other race/ethnic groups: The MASALA and MESA studies

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Abstract

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AUTHOR CONTRIBUTIONS

MAR performed the analytic calculations wrote the initial draft of the manuscript. AK, MCA, JP, MB, MHC, MJB, and SSV contributed to the design and writing of the manuscript.

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DECLARATION OF CONFLICTS OF INTEREST

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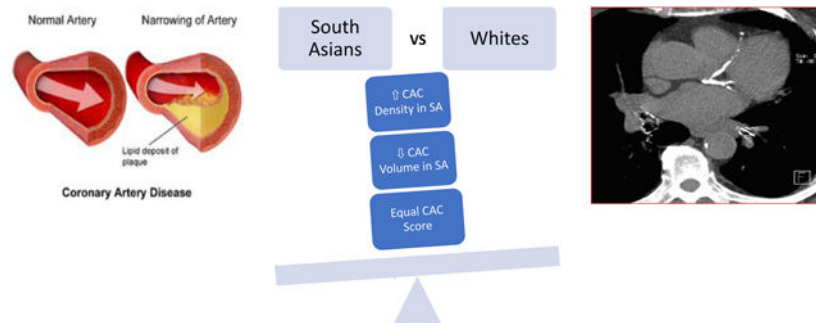
Background and aims: South Asians (SA) experience disproportionately higher rates of atherosclerotic cardiovascular disease (ASCVD) events than non-Hispanic whites and several other Asian groups. The coronary artery calcium (CAC) Agatston score may not capture the unique characteristics of coronary plaque in SA. We therefore evaluated the prevalence and patterns of advanced CAC measures (specific coronary vessel involvement, CAC volume and density) in SA *versus* other race/ethnicities.

Methods: We combined data from the Mediators of Atherosclerosis in South Asians Living in America (MASALA) and Multi-Ethnic Study of Atherosclerosis (MESA) cohorts. We used multivariable-adjusted linear regression models to compare advanced CAC measures between SA and other ethnicities.

Results: Our analyses included 7,625 individuals (810 SA, 2,622 whites, 1,893 African Americans, 1,496 Hispanics, 803 Chinese Americans) with mean (SD) age 62 (10) years and 48% men. In adjusted analyses, compared to non-Hispanic whites (NHW), SA had lower overall CAC volume [beta coefficient (95% CI)] [-0.46 (-0.62,-0.29)] but higher overall CAC density [0.14 (0.11,0.18)]. These trends were similar when SA were compared to non-whites (Hispanics, Chinese Americans, and African Americans). SA had higher overall [0.07 (0.03,0.12)] and right coronary artery [0.09 (0.03,0.16)] CAC density compared to non-whites, while CAC volume was not significantly different between these two groups.

Conclusion: SA have lower CAC volume compared to NHW but similar compared to non-whites. Overall CAC density is higher among SA compared to NHW and non-whites. Future longitudinal studies of ASCVD events are required to confirm the prognostic significance of these findings among SA.

Graphical Abstract



Introduction

The American Heart Association/American College of Cardiology/Multi-Society guideline recommends assessment of atherosclerotic cardiovascular disease (ASCVD) risk enhancing factors to guide the initiation of statin therapy among individuals at borderline or intermediate estimated risk.^{1,2} Recognizing the high prevalence of cardiovascular risk factors and disproportionately higher rates of ASCVD events among South Asian (SA) populations compared to non-white populations,³⁻⁶ the guideline endorses SA ethnicity as an ASCVD risk enhancing factor to guide decisions around preventive therapy in this high-risk group.

Coronary artery calcium (CAC) is a marker of subclinical atherosclerosis and has been shown to be prognostic of incident ASCVD events in several race/ethnic groups.⁷ In a prior study from the Mediators of Atherosclerosis in South Asians Living in America (MASALA) cohort, SA men were demonstrated to have similar overall CAC burden as non-Hispanic whites (NHW) but higher CAC burden compared to other race/ethnic groups, while SA women had a similar CAC burden compared to women of other race/ethnicities.⁸

The classic Agatston score, however, may not be sufficiently informative, and additional plaque characteristics beyond the classic Agatston's CAC score may help assess ASCVD risk. For example, a prior study in the Multi-Ethnic Study of Atherosclerosis (MESA) showed that CAC volume was associated with incident ASCVD, while CAC density was inversely associated with ASCVD after accounting for CAC volume and traditional risk factors.⁹ In another MESA study, a higher number of coronary vessels with calcified plaque was associated with incident ASCVD events independent of cardiovascular risk factors and CAC score.¹⁰

No prior study has evaluated advanced CAC measures (CAC volume, CAC density, and number of vessels with calcified plaque) among SA compared with other ethnic groups. The MASALA study also has information on CAC volume, calculated density score, and number and type of coronary vessels with calcified plaque. We therefore conducted a cross-sectional comparison of CAC volume, CAC density, and number and type of coronary vessels with calcified plaque among SA in the MASALA study *versus* 4 other race/ethnic groups in the MESA study (NHW, African American, Hispanic, and Chinese-American).

Materials and methods

Study design

Full details of the design and methods of the MASALA and MESA studies have been reported elsewhere.^{11,12} Briefly, MASALA is a community-based prospective cohort study of 906 asymptomatic US adults of SA ancestry without clinical ASCVD, who were enrolled from 2 clinical sites (San Francisco Bay Area at the University of California, San Francisco (UCSF) and the greater Chicago area at Northwestern University (NWU)). SA ancestry was defined as having at least 3 grandparents born in India, Pakistan, Bangladesh, Nepal, or Sri Lanka. The first study examination began in October 2010, and final participant enrollment ended in March 2013. The study protocol was based on MESA. The MASALA study protocol was approved by the institutional review boards of University of California, San Francisco and Northwestern University. All participants provided a written informed consent.¹¹

MESA is a multi-ethnic, community-based, prospective cohort study of 6,814 men and women aged 45 to 84 years who were free from clinical ASCVD at baseline. Participants were enrolled between July 2000 and September 2002 at 6 field centers in the US and identified themselves as NHW, African American, Hispanic, or Chinese American. The study was approved by the institutional review boards at each center. All MESA participants provided written informed consent.¹²

Inclusion/exclusion criteria—MASALA participants aged <45 years (n=94) were excluded from the analysis as the minimum age of MESA participants at enrollment was 45 years.

Assessment of CAC measures—Details on the CAC quantification methods implemented in the two studies have been previously reported. In MESA, CAC was measured using either an electron-beam CT (at the Chicago, Los Angeles, and New York centers) or a multidetector CT (at the Baltimore, Forsyth County, and St. Paul centers).¹² All images were interpreted at the Los Angeles Biomedical Research Center, Torrance, CA. In MASALA, CAC was assessed using a cardiac-gated electron-beam CT (San Francisco center) or multidetector CT (both San Francisco and Chicago centers).⁸ All images were analyzed at the Los Angeles Biomedical Research Center according to MESA study methods.¹¹ In both studies, CAC scans were interpreted blinded to race/ethnicity and quantified using the Agatston scoring system.¹³ In MESA, intraobserver and interobserver agreements for CAC were excellent (kappa statistics, 0.93 and 0.90, respectively). These estimates are likely to be similar for the MASALA study given that identical scanning protocols were used and images were interpreted at the same reading center. To facilitate comparisons between the two studies, we only utilized CAC measurements from the first coronary computed tomography scan in MESA, as MASALA participants were scanned only once, while MESA participants were scanned twice.

CAC score was quantified using the Agatston scoring method as summation of the product of plaque area and density weight factor based on CT attenuation (130 to 199 Hu =1; 200 to 299 = 2; 300 to 399 = 3; 400 Hu = 4). The Agatston CAC score for calcified plaques was quantified for each major epicardial vessel [left main (LM), left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA)].¹⁴ Overall Agatston CAC score was calculated as the summation of Agatston CAC score for each of the four epicardial vessels. Overall CAC volume score was calculated as the summation of volume of plaques across all calcified lesions for each epicardial vessel.¹⁴ To calculate CAC density, the area score was first derived by dividing the volume score by slice thickness (3 mm for the electron-beam CT scanners and 2.5 mm for the multidetector CT scanners). Agatston CAC score was then divided by the area score to calculate CAC density score both overall and for each epicardial vessel.⁹

Covariates—Information on sociodemographic characteristics, tobacco use, family history of coronary heart disease, and medication use was collected using validated questionnaires.¹² Systolic and diastolic blood pressures were measured three times using an automated sphygmomanometer and the mean of the last two measurements was used for analyses. Lipid profile, plasma glucose and insulin levels were measured in blood samples collected at baseline and after a 12-hour overnight fast. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dL or the use of a glucose-lowering medication. Prediabetes was defined as fasting plasma glucose ≥ 100 and <126 mg/dL. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated as the product of fasting insulin and fasting glucose.

Statistical analysis—Baseline demographics and cardiovascular risk factors were described for each race/ethnicity. Continuous variables were summarized using mean (SD)

or median (IQR) and compared using ANOVA. Categorical variables were summarized using count (percentage) and compared using chi-square testing.

Median CAC volume and density (overall and per coronary vessel), and number of coronary vessels with calcified plaque were summarized for each race/ethnicity. CAC volume was log transformed as $\ln(\text{CAC} + 1)$ to account for those with CAC volume of 0. CAC density was also log-transformed to ensure normality of the data.

We studied the association of race/ethnicity with advanced CAC measures using 2 reference categories for race/ethnicity. In the first analysis, we compared each of SA, African Americans, Hispanics, and Chinese Americans to NHW. In the second analysis, we compared SA to non-whites (i.e. African Americans, Hispanics, and Chinese Americans). For each of these analyses, we performed multivariable linear regression models. Models were adjusted for age, sex, education, lipid lowering medication use, antihypertensive medication use, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, cigarette smoking status, and diabetes mellitus. Results for CAC volume were additionally adjusted for CAC density and results for CAC density were additionally adjusted for CAC volume consistent with the prior study by Criqui et al.⁹

Linear regression models yielded beta coefficients, which represent the absolute difference in CAC compared to the reference group. For example, in the analysis of CAC volume among SA vs. non-whites, the beta coefficient of SA can be interpreted as the difference in CAC volume between SA and non-whites adjusting for the above covariates.

In a sensitivity analysis, we 1) stratified results by sex, 2) excluded individuals taking lipid-lowering therapy (n=1,349), and evaluated those with Agatston CAC score >1000 (n=525). A *p* value <0.05 was considered statistically significant. All analyses were performed using Stata version 13 (StataCorp. 2011, College Station, TX).

Results

Our analyses included 7,625 individuals (810 SA, 2,622 whites, 1,893 African Americans, 1,496 Hispanics, 803 Chinese Americans) with mean (SD) age 62 (10) years and 48% men. SA participants were more likely to be younger, male, have high education, and more likely to report being never smokers compared to the other race/ethnic groups in MESA. SA were also more likely to be on cholesterol lowering medications and have diabetes (all *p*<0.05) (Table 1).

Compared to NHW, SA had lower overall CAC volume but higher CAC density in unadjusted analyses. These trends were similar in individual coronary vessels (Table 2).

South Asians vs. non-Hispanic whites

There was no significant difference between CAC volume for SA vs. NHW prior to adjustment for CAC density. In analyses that further adjusted for CAC density, SA had lower overall CAC volume [beta coefficient (95% CI)] [-0.46 (-0.62,-0.29)] and CAC volume in all epicardial vessels except LM, which was non-significantly lower compared to NHW (Figure 1). SA had higher overall CAC density [0.14 (0.11,0.18)] compared to NHW. These

trends were similar for all epicardial vessels (Figure 2). SA also had a higher number of coronary vessels with calcified plaque compared to NHW [0.18 (0.07,0.28)] ($p<0.05$).

African Americans, Hispanics, and Chinese Americans vs. non-Hispanic whites

In general, African Americans, Hispanics, and Chinese Americans had lower CAC volume but higher CAC density compared to NHW both overall and per coronary vessel.

South Asians vs. non-whites

In adjusted analyses, SA had higher overall [0.07 (0.03,0.12)] and RCA [0.09 (0.03,0.16)] CAC density compared to non-whites, while CAC volume was not significantly different between the two groups. SA had a higher number of coronary vessels with calcified plaque compared to non-whites [0.29 (0.17,0.40)] ($p<0.05$).

Sensitivity analyses

In sex-stratified analyses, SA women had lower left main (LM) CAC volume compared to NHW women, while results for other epicardial vessels were not significant. SA women had higher CAC density compared to NHW women for all epicardial vessels except for left circumflex (LCx). SA men had lower CAC volume and higher CAC density for all epicardial vessels except LM (Supplementary Table 1). There was no significant interaction between gender and race/ethnicity ($p>0.05$).⁷ Analyses excluding participants on lipid-lowering medications generally yielded similar results except that LCx and RCA CAC volume were not significantly lower, while LM CAC density was not significantly higher among SA compared to NHW. Number of vessels with calcified plaque remained non-significantly higher among SA compared to NHW (Supplementary Table 2). In general, there was no significant interaction between lipid-lowering medication use and race/ethnicity for all outcomes except for RCA CAC volume. Among those with Agatston CAC score >1000, both overall and individual CAC density remained significantly higher among SA compared to NHW, while all results for CAC volume were no longer significant, and the number of calcified vessels with calcified plaque remained nonsignificant. (Supplementary Table 3).

Discussion

In our study, we found that SA, Hispanics, Chinese Americans, and African Americans have significantly lower CAC volume but higher CAC density compared to NHW. SA also have significantly higher CAC density compared to non-whites. SA have a higher number of vessels with calcified plaque compared to NHW and non-whites.

SA experience disproportionately higher rates of ASCVD events compared to whites and non-whites.³⁻⁶ Prior studies of subclinical atherosclerosis showed that among patients with angina and heart disease, SA had more diffuse calcification and plaque burden, greater coronary artery stenosis, more proximal and longer lesions, and also smaller coronary artery diameter compared to Europeans.¹⁵⁻¹⁸ In the present study, we examined subclinical coronary atherosclerosis measures beyond the classic Agatston CAC score including CAC volume, CAC density, and number of coronary arteries with calcified plaque.¹⁵⁻¹⁸ Such

measures in addition to CAC score have been shown to have prognostic implications.¹⁹ Importantly, we found that SA have higher CAC density compared to whites and non-whites. CAC density is inversely associated with ASCVD after adjusting for CAC volume suggesting that higher coronary plaque density may reflect more stable plaques that are less likely to rupture.⁹ These results were consistent even after excluding those on lipid lowering therapy, which has been shown to promote plaque calcification.²⁰ SA have lower overall CAC volume compared to NHW adjusting for CAC density. Of note, overall CAC volume was not significantly different between SA and NHW when the model was not adjusted for CAC density.

Prior studies of Agatston CAC score showed that SA men and women have a similar burden of CAC compared to NHW men and women.⁸ The Agatston CAC score is upweighted for CAC density such that more dense plaques contribute to a higher CAC score. While higher Agatston CAC score and CAC volume are associated with higher risk of ASCVD events, higher CAC density is inversely associated with ASCVD.⁹ Therefore, the Agatston CAC score may mask important differences in plaque physiology that could be better assessed using CAC volume and CAC density. Our study shows that SA have a lower CAC volume but higher CAC density, which may result in a similar Agatston CAC score for SA and NHW.

Our observation of a lower CAC volume but a higher CAC density in SA compared to NHW could be explained by several factors. MASALA participants may have better risk factor control than other SA²¹ due to several factors including a higher socioeconomic status, better access to healthcare, less smoking, and higher use of preventive medications such as statins. Cardiometabolic risk remains high among SA starting from an early age and there is a tendency for risk factors to cluster. MASALA participants were required to be free of clinical ASCVD in order to be included in the study, and therefore SA with premature ASCVD were excluded. Prevalence and incidence estimates of ASCVD among SA that are cited in the literature were derived from studies that were conducted almost three decades ago (e.g. UK)²² or in countries where SA still comprise a relatively low-income group (e.g. Italy).²³ However, a recent analysis from a large integrated health system found that SA had twice the risk of heart disease events compared to NHW and other race/ethnic groups^{6,24} Until information on incident ASCVD outcomes in MASALA becomes available, the prognostic implications of these findings cannot be determined. The present study results, therefore, should not be taken to suggest that SA are truly a low risk group. Continued efforts are required to screen and treat cardiovascular risk factors according to established guidelines to prevent the occurrence of ASCVD.

Our study has important limitations. MASALA is still accumulating ASCVD event data among SA, which precludes studying the association between advanced CAC measures and incident ASCVD events. The sample size of the SA population was relatively small, which may underpower analyses comparing SA to other race/ethnic groups, especially in analyses excluding individuals on lipid-lowering medication. Medication use and risk factors were assessed only at the time of study enrollment, and we do not currently have information on prior use of medications or risk factor profile. MASALA was initiated 10 years after MESA, which may partly explain the differences in subclinical atherosclerosis and cardiovascular

risk factor profile between SA and other race/ethnic groups in MESA. For example, there has been a marked increase in statin use between 2000 and 2010. There has also been a decreasing prevalence in cigarette use as a result of antitobacco laws. SA in MASALA were younger and had a high socioeconomic status, and therefore, our results may not be generalizable to all SA both in and outside the U.S. Lastly, there remains the possibility of residual confounding in this epidemiologic cohort study.

In conclusion, SA, Hispanics, Chinese Americans, and African Americans have lower CAC volume but higher CAC density compared to NHW. Future longitudinal studies of ASCVD events are required to confirm the prognostic significance of these findings among SA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- Overall CAC density was higher among SA compared to NHW and non-whites.
- Future longitudinal studies of ASCVD events are required to confirm the prognostic significance of these findings.

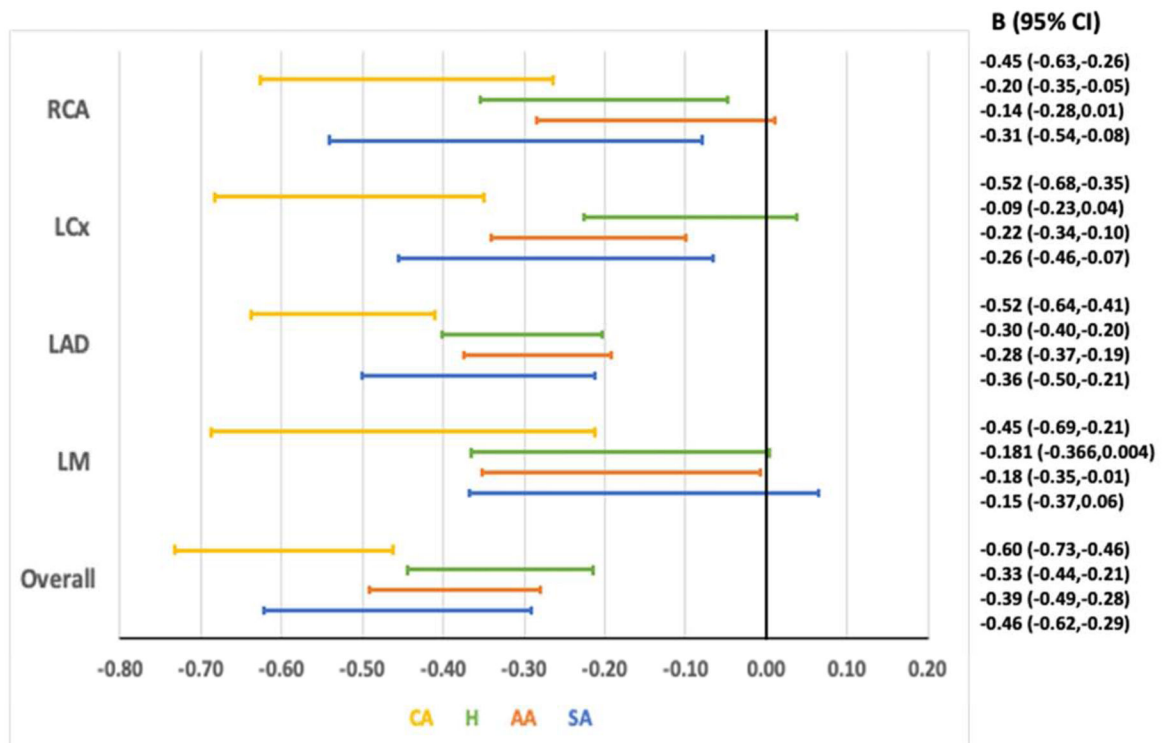


Figure 1.

Multivariable-adjusted beta coefficients (95% confidence interval) for the association of race/ethnicity (South Asians, African Americans, Hispanics, Chinese Americans vs. non-Hispanic whites as reference group) and CAC volume*

SA = South Asians; AA = African Americans; H = Hispanics; CA = Chinese Americans; CAC = coronary artery calcium; LM = left main; LAD = left anterior descending; LCx = left circumflex; RCA = right coronary artery.

All CAC measures were log-transformed.

Model is adjusted for age, sex, education, lipid lowering medication use, antihypertensive medication use, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, cigarette smoking status, diabetes mellitus. Results for CAC volume are additionally adjusted for CAC density. Results for CAC density are additionally adjusted for CAC volume.

Beta coefficients represent the difference in CAC compared to the reference category. For example, in this analysis of CAC volume among SA vs. non-Hispanic whites, the beta coefficient of SA is interpreted as the difference in CAC volume between SA and non-Hispanic whites.

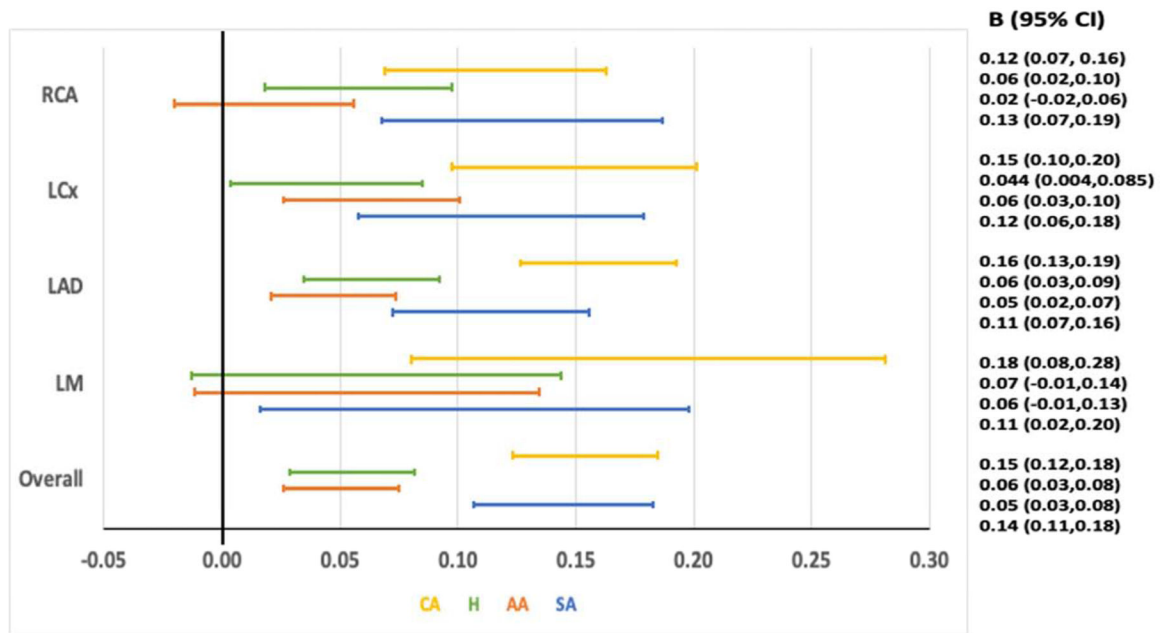


Figure 2.

Multivariable-adjusted beta coefficients (95% confidence interval) for the association of race/ethnicity (South Asians, African Americans, Hispanics, Chinese Americans vs. non-Hispanic whites as reference group) and CAC density

SA = South Asians; AA = African Americans; H = Hispanics; CA = Chinese Americans; CAC = coronary artery calcium; LM = left main; LAD = left anterior descending; LCx = left circumflex; RCA = right coronary artery.

^bAll CAC measures were log-transformed.

Model is adjusted for age, sex, education, lipid lowering medication use, antihypertensive medication use, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, cigarette smoking status, diabetes mellitus. Results for CAC volume are additionally adjusted for CAC density. Results for CAC density are additionally adjusted for CAC volume.

Beta coefficients represent the difference in CAC compared to the reference category. For example, in this analysis of CAC volume among SA vs. non-Hispanic whites, the beta coefficient of SA is interpreted as the difference in CAC volume between SA and non-Hispanic whites.

Table 1. Baseline characteristics of the study population by race/ethnicity, MESA and MASALA at the baseline study examinations

	South Asians (N=811)	Non-Hispanic whites (N=2,622)	African Americans (N=1,893)	Hispanic (Latinos) (N=1,496)	Chinese Americans (N=803)
Age, years	57 (9)	63 (10)	62 (10)	61 (10)	62 (10)
Men	429 (53)	1,259 (48)	843 (45)	721 (48)	390 (49)
Education greater than bachelor	697 (87)	1,297 (50)	636 (34)	148 (10)	312 (39)
Cigarette smoking status					
Never	670 (83)	1,157 (44)	850 (45)	807 (54)	604 (75)
Former	113 (14)	1,157 (44)	691 (37)	486 (32)	153 (19)
Current	27 (3)	301 (12)	338 (18)	203 (14)	45 (6)
Systolic blood pressure, mmHg	126 (16)	123 (20)	132 (22)	127 (22)	125 (22)
Antihypertensive medication use	264 (33)	867 (33)	951 (50)	487 (33)	231 (29)
High-density lipoprotein cholesterol, mg/dL	50 (13)	52 (16)	52 (15)	48 (13)	49 (13)
Low-density lipoprotein cholesterol, mg/dL	111 (32)	117 (30)	117 (33)	120 (33)	115 (29)
Triglycerides, mg/dL	132 (72)	133 (90)	105 (69)	157 (101)	143 (85)
Total cholesterol, mg/dL	187 (37)	196 (35)	190 (36)	198 (37)	193 (32)
Cholesterol lowering medication use	249 (31)	479 (18)	309 (16)	196 (13)	116 (15)
Fasting plasma glucose, mg/dL	104 (25)	91 (22)	100 (32)	104 (39)	99 (28)
Fasting plasma insulin, mu/L	7.7 (10.2)	9.2 (5.6)	11.4 (25.5)	11.8 (15.4)	9.5 (12.3)
HOMA-IR	3.6 (6.3)	2.2 (1.7)	3.0 (10.5)	3.2 (6.2)	2.4 (3.2)
Diabetes mellitus	169 (28)	158 (6)	332 (18)	264 (18)	105 (13)
Prediabetes	248 (35)	334 (13)	348 (21)	283 (22)	164 (22)

Continuous variables are summarized as mean (standard deviation) or median (interquartile range) and compared using ANOVA or median test as appropriate. Categorical variables are summarized as count (percentage) and compared using chi-square test.

All *p*-values for comparison are <0.001.

Table 2.

Coronary artery calcium measures by race/ethnicity

	South Asians (N=811)	Non-Hispanic whites (N=2,622)	African Americans (N=1,893)	Hispanic (Latinos) (N=1,496)	Chinese Americans (N=803)
CAC volume (mm³)					
Overall	0 (0–69)	11 (0–140)	0 (0–50)	0 (0–56)	0 (0–66)
LM	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
LAD	0 (0–36)	0 (0–74)	0 (0–27)	0 (0–28)	0 (0–42)
LCx	0 (0–0)	0 (0–13)	0 (0–0)	0 (0–0)	0 (0–0)
RCA	0 (0–0)	0 (0–11)	0 (0–0)	0 (0–0)	0 (0–0)
CAC density (Hu)					
Overall	3.1 (2.3–3.5)	2.8 (2.3–3.1)	2.8 (2.3–3.2)	2.9 (2.1–3.3)	3.1 (2.5–3.5)
LM	3.4 (2.0–4.0)	3.0 (2.0–3.3)	3.0 (2.0–3.3)	3.0 (2.0–3.7)	3.0 (2.0–4.0)
LAD	3.2 (2.1–3.7)	2.9 (2.3–3.2)	2.9 (2.2–3.3)	3.0 (2.0–3.4)	3.2 (2.5–3.7)
LCx	3.0 (2.0–3.5)	2.7 (2.0–3.2)	2.8 (2.0–3.3)	2.7 (2.0–3.3)	3.0 (2.0–3.6)
RCA	2.7 (2.0–3.4)	2.5 (1.9–2.9)	2.5 (1.8–3.0)	2.5 (2.0–3.0)	2.7 (2.0–3.3)
Number of coronary arteries with calcified plaque					
0, N (%)	415 (51)	1,138 (43)	1,040 (55)	835 (56)	406 (51)
1, N (%)	127 (16)	473 (18)	294 (16)	239 (16)	162 (20)
2, N (%)	84 (10)	346 (13)	199 (11)	172 (12)	110 (14)
3, N (%)	103 (13)	423 (16)	215 (11)	176 (12)	92 (11)
4, N (%)	82 (10)	242 (9)	145 (8)	74 (5)	33 (4)

Hu = Hounsfield unit; Au = Agatston unit CAC = Coronary artery calcium; LM = left main; LAD = left anterior descending; LCx = left circumflex; RCA = right coronary artery
 Continuous variables are summarized as median (interquartile range).