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Authors

Al Rifai, Mahmoud
Kandula, Namratha
Patel, Jaideep
et al.

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Association of Coronary Artery Calcium Density and Volume with Predicted Atherosclerotic Cardiovascular Disease Risk and Cardiometabolic Risk Factors in South Asians: The Mediators of Atherosclerosis in South Asians Living in America (MASALA) Study

Mahmoud Al Rifai, MD MPH[1], **Alka M. Kanaya, MD**[2], **Namratha R Kandula, MD MPH**[3], **Jaideep Patel, MD**[4], **Mouaz H. Al-Mallah, MD MSc**[5], **Matthew Budoff, MD**[6], **Miguel Cainzos-Achirica, MD MPH**[7], **Michael H. Criqui, MD, MPH**[8,9], **Salim S. Virani, MD PhD**[10,1,*]

[1]Section of Cardiology, Department of Medicine, Baylor College of Medicine, Houston, TX

[2]Department of Medicine, University of California, San Francisco, San Francisco, CA, USA

[3]Feinberg School of Medicine, Division of General Internal Medicine, Northwestern University, Chicago, IL, USA; Feinberg School of Medicine, Department of Preventive Medicine, Northwestern University, Chicago, IL, USA

[4]Pauley Heart Center, Division of Cardiology, Virginia Commonwealth University Medical Center, Richmond, VA

[5]Department of Cardiac Imaging, Houston Methodist Hospital, Houston, TX

[6]Division of Cardiology, Los Angeles Biomedical Research Institute, Torrance, CA, USA;

[7]Division of Cardiovascular Prevention and Wellness, Department of Cardiology, Houston Methodist DeBakey Heart & Vascular Center, Center for Outcomes Research, Houston Methodist, Houston (TX), USA

[8]Division of Preventive Medicine, Department of Family Medicine and Public Health

[9]University of California, San Diego School of Medicine, CA, USA

[10]Division of Cardiology, Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine, Houston, TX

Abstract

Background: Individuals of South Asians (SA) ancestry are predisposed to higher risk of atherosclerotic cardiovascular disease (ASCVD). Coronary artery calcium (CAC) volume and

[*]**Corresponding author:** Salim S. Virani, MD PhD, virani@bcm.edu, 713-440-4410, Baylor College of Medicine, 2002 Holcombe Blvd., Houston, TX 77030.

density can identify coronary plaque characteristics unique to SA that may provide important prognostic information to identify high risk individuals beyond traditional CAC scores.

Methods: We used data from the Mediators of Atherosclerosis in South Asians Living in America (MASALA). CAC density and volume were calculated according to established protocols. ASCVD risk was estimated using the pooled cohort equations (PCE). Multivariable-adjusted linear regression models were used to study the association between the PCE and advanced CAC measures, and between cardiovascular risk factors and these CAC density and volume.

Results: Our analyses included 1,155 participants (mean age 57 (SD 9) years, 52% men) with information on CAC measures. After multivariable-adjustment, the PCE was associated with both CAC density (β 0.24, 95% CI 0.12,0.35) and CAC volume (β 0.43, 95% CI 0.38,0.48). High-density lipoprotein cholesterol was directly associated with CAC density while waist circumference was inversely associated with it. Body mass index, hypertension status, statin use, diabetes, and HOMA-IR were all directly associated with CAC volume.

Conclusion: Estimated ASCVD risk is associated with both CAC volume and density among SA. Different cardiometabolic risk factors are associated with CAC density and volume. Future longitudinal studies are required to demonstrate the interrelationship of advanced measures and cardiovascular risk factors with incident ASCVD outcomes.

Keywords

South Asians; coronary artery calcium; coronary artery calcium density; cardiovascular risk factors

INTRODUCTION

South Asian individuals experience disproportionately higher atherosclerotic cardiovascular disease (ASCVD) event rates compared to other racial/ethnic groups.[1] Current American Heart Association/American College of Cardiology/Multisociety (AHA/ACC/MS) cholesterol guidelines recommend 10-year ASCVD risk estimation using the pooled cohort equations (PCE) as a first step to guide a clinician-patient risk discussion regarding initiation of statin therapy.[2–4] While SA ethnicity was recommended to be a “risk-enhancing factor, notably SA were not included in the cohorts used to derive the PCE, and therefore, the performance of these risk calculators among SA is not currently known. However, prior studies have demonstrated a tendency for the PCE to overestimate risk among SA.[5,6]

Measures of subclinical atherosclerosis can be informative as they are independently associated with incident ASCVD outcomes.[7] Coronary artery calcium (CAC) measures calcified coronary plaque which correlates with overall plaque burden. Importantly CAC can be used for both discrimination and reclassification of ASCVD and is endorsed by major guidelines for use in clinical practice among selected intermediate and borderline risk individuals.[3,4,8–10] Estimated 10-year ASCVD risk using the PCE has been shown to correlate with CAC burden among SA in MASALA.[11]

The classic Agatston CAC score is derived by multiplying plaque area by a density weight factor. More dense plaques are thought to be more stable and less likely to rupture as opposed to less dense plaques. In a seminal study by Criqui et al, CAC density was found to be inversely correlated with incident ASCVD, while CAC volume (and similarly Agatston CAC score) was directly associated with incident ASCVD.[12]

It is important to evaluate CAC volume and CAC density separately as the Agatston CAC score may not capture these important differences in coronary plaque characteristics. Prior studies have shown that while Agatston CAC score is similar comparing SA and non-Hispanic White adults,[13] overall CAC volume is lower and CAC density is higher among SA[14] and there are important differences by sex. In the present study, we evaluated the association between PCE and CAC volume or density among SA. Furthermore, we assessed the association of traditional and novel cardiovascular risk factors with CAC volume and density among SA.[15,16]

METHODS

Study Design

Full details of the design and methods of MASALA study have been reported elsewhere.[17] Briefly, MASALA is a community-based prospective cohort study that enrolled 906 asymptomatic US adults of SA ancestry without clinical ASCVD from two 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. An additional 258 SA participants were recruited between 2017 and 2018. The 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.

Exclusion Criteria

We excluded participants with missing information on CAC (n=9). In analyses of CAC density, we excluded individuals with CAC 0 (n=615).

Assessment of CAC Volume and CAC Density

CAC was assessed using a cardiac-gated electron-beam CT (San Francisco center) or multidetector CT (both San Francisco and Chicago centers).[13] All images were analyzed at the Los Angeles Biomedical Research Center according to MESA study methods.[17] CAC volume was calculated as the summation of volume of plaques across all calcified lesions.[18] The average area score was first derived by dividing the total volume score by slice thickness. The Agatston score[18] was then divided by the area score to derive CAC density.[12]

Assessment of Covariates

Information on sociodemographic characteristics, tobacco use, family history of coronary heart disease, and medication use was collected using validated questionnaires. Intentional exercise in metabolic equivalent task-minutes per week was assessed using the Typical Week's Physical Activity Questionnaire.[19] Information on dietary patterns was collected using the Study of Health Assessment and Risk in Ethnic groups South Asian food frequency questionnaire (FFQ), which was developed and validated in SA living in Canada. The FFQ consisted of 163 items, with 61 items unique to the SA diet, which evaluated usual eating habits, frequency, and serving sizes over the past year.[20,21]

Systolic and diastolic blood pressures (SBP and DBP respectively) were measured three times using an automated sphygmomanometer and the mean of the last two measurements was used. Lipid profile and plasma glucose levels were measured in blood samples collected at baseline and after a 12-hour overnight fast. Hypertension was defined as SBP ≥140 mm Hg, DBP ≥90 mm Hg, or taking a medication for hypertension. Diabetes was defined as a fasting glucose of ≥126 mg/dl, or a post-challenge glucose ≥200 mg/dl, or by the use of diabetes medications (oral agents and/or insulin). The homeostasis model assessment of insulin resistance (HOMA-IR) was used as a surrogate of insulin resistance and calculated as $insulin_0$(mIU/mL) × $glucose_0$ (mmol/L)/22.5. Hepatic fat attenuation was measured using computed tomography.[22] Lp(a) levels were measured by particle-enhanced immunonephelometry on a BNII nephelometer.[23]

ASCVD risk was calculated using the PCE which is comprised of age, sex, high-density lipoprotein cholesterol (HDL-C), total cholesterol, SBP, diabetes, antihypertensive medication use, and cigarette smoking. In accordance with the AHA/ACC/MS guideline,[3] we used equations for non-Hispanic Whites to calculate predicted risk for SA.

Statistical Analysis

Baseline characteristics were presented for the overall study population and stratified by sex. Continuous variables were summarized using mean (SD) or median (IQR) and compared using ANOVA or Kruskal-Wallis testing respectively depending on the normality of the data. Categorical variables were summarized using count (percentage) and compared using chi-squared tests.

CAC volume and density were log-transformed as log (CAC volume +1) and log(CAC density) and standardized by their respective standard deviation. Estimated ASCVD risk using the PCE was log-transformed as well.

We used multivariable-adjusted linear regression analyses to study the association of the PCE with CAC volume and density. Results were adjusted for education, annual family income, birth country, years lived in the U.S. and statin medication use. Results for CAC density were additionally adjusted for CAC volume while results for CAC volume were additionally adjusted for CAC density.[12] We also stratified results by sex.

We also evaluated the association between each cardiovascular risk factors and CAC volume and density using multivariable-adjusted linear regression models adjusted for age, sex,

education, annual family income, birth country, and years lived in the U.S. Results for CAC density were additionally adjusted for CAC volume while results for CAC volume were additionally adjusted for CAC density.[12] Additionally, we stratified results by sex and excluded statin users as a sensitivity analysis.

A two-sided p-value of <0.05 will be considered statistically significant. All analyses were conducted using Stata/IC version 16 (StataCorp, College Station, Texas).

RESULTS

Our study population consisted of 1,155 participants with mean age 57 (SD 9) years, 52% men, 56% with a greater than Bachelor's degree, and 62% with annual family income >$100k. Compared to men, women were younger, had higher total cholesterol, LDL-C, HDL-C, Lp(a), liver fat attenuation (indicating less fatty liver), and more likely to have family history of CHD. As expected, women had a lower ASCVD risk score and CAC volume, were less likely to be on a statin, have diabetes, hypertension, or to be currently smokers compared with men (all p<0.05) (Table 1).

In unadjusted models, the PCE was associated with both CAC density and volume. After multivariable-adjustment, the PCE remained associated with both CAC density (β 0.24, 95% CI 0.12,0.35) and CAC volume (β 0.43, 95% CI 0.38,0.48) though results were numerically higher for CAC volume. Similar results were obtained in sex-stratified models except that the PCE was not significantly associated with CAC density among women (β 0.14, 95% CI −0.15,0.43) (Table 2).

In multivariable-adjusted models, HDL-C was directly associated with CAC density while waist circumference was inversely associated. For CAC volume, direct association were seen with BMI, hypertension, statin use, diabetes, and HOMA-IR (Table 3).

In sex-stratified analyses, waist circumference was inversely associated with CAC density in both sexes. Waist circumference, BMI, and statin use were directly associated with CAC volume among women, while hypertension, diabetes, and HOMA-IR were directly associated with CAC volume among men (results not shown). Analyses excluding statin users generally yielded similar results except that hypertension and HOMA-IR were inversely associated with CAC density while HDL-C was inversely associated with CAC volume and family history of CHD was positively associated with CAC volume.

DISCUSSION

In a contemporary cohort of SA in the U.S., the PCE was significantly associated with both CAC volume and density. Different cardiometabolic risk factors were significantly associated with CAC volume and density.

A previous study demonstrated that the Agatston CAC score is associated with the PCE among SA.[11] Our study demonstrated that the PCE is significantly associated with both CAC volume and density, As the PCE remains the first step for guiding the clinician-patient risk discussion,[3] the additional information offered by CAC volume and density could be

used to further refine absolute ASCVD risk estimates among SA. Our study could provide insight about the potential prognostic utility of the PCE among SA using CAC volume and density as surrogate outcomes until information on incident ASCVD events becomes available. However, further studies of longitudinal events in MASALA are required to corroborate the significance of findings in the current study.

Our study found a positive association between HDL-C and CAC density. Prior studies have demonstrated that the association of LDL-C and high-sensitivity C-reactive with CAC is attenuated by HDL-C.[25,26] While we could not evaluate mechanistic pathways linking HDL-C with CAC density, presumably higher HDL-C may result in more dense coronary plaques that more stable and therefore less likely to rupture. We also found that higher waist circumference was associated with lower CAC density in both men and women while higher BMI and waist circumference were associated with higher CAC volume among women only. In a study by Park et al, obesity as defined by higher waist circumference and BMI were both associated with presence of CAC.[27] Obesity is also a well-established risk factor for ASCVD.[28] Our results suggest that obesity could result in less dense and larger plaque which are intrinsically more prone to rupture resulting in clinical manifestations of ASCVD. The association between hypertension and CAC is well-established.[29] Our study found that hypertension was associated with CAC volume among men only, while there was no significant association with CAC density. It is difficult to distinguish the effects of hypertension on size and density of coronary plaques, but we surmise that hypertension may result in larger plaques regardless of how dense they are.

Impaired glucose metabolism as assessed by HOMA-IR and diabetes were directly associated with CAC volume in our study, but among men only. These results were consistently demonstrated among men only. Prior studies have demonstrated that HOMA-IR and diabetes are strongly associated with CAC.[30,31] Unique to SA, the metabolic syndrome is highly prevalent and may play a central role in the pathogenesis of ASCVD in this racial/ethnic group.[32] The results of our study suggest that glucose dysregulation among SA can result in larger coronary plaques that predispose to ASCVD.

Lastly, we found that statin use was associated with larger coronary plaques as measured by CAC volume. This result was surprising given that statin use is associated with lower plaque volume.[33] Statins are hypothesized to reduce non-calcified plaque burden resulting in more dense and stable coronary plaques that are less likely to rupture. However, we did not find a significant association between statin use and CAC density. It is difficult to establish a causal effect between statin use and advanced CAC measures in the present study though we posit that our results could be explained by the observational nature of our data which may be limited by reverse causation and confounding by indication (indication bias), when considering the effects of medication use. MASALA participants who were on statin therapy at baseline were presumably started on these medications due to their higher risk status. Therefore, those who are treated are likely the ones who have larger coronary plaques to begin with. Consistent with this, we found a direct association between CAC volume and estimated ASCVD risk using the PCE which is used to guide statin therapy. After excluding statin users, we found that hypertension and HOMA-IR were inversely associated with CAC density and HDL-C was inversely associated with CAC volume. Interestingly, family history

of CHD was directly associated with CAC volume consistent with our prior work showing a strong association between family history of CHD and high CAC burden among SA.[34]

Our study has important limitations. First, MASALA is still accruing ASCVD event data among SAs, and therefore we could not examine the association between advanced CAC measures and incident ASCVD outcomes. Second, the sample size of the SA population was relatively small, which may underpower analyses. SAs in MASALA may not be representative of all SA given their high socioeconomic status and high prevalence of statin medication use. Lastly, the cross-sectional nature of our study precludes any inferences regarding causality between cardiovascular risk factors and advanced CAC measures.

In conclusion, CAC volume is directly associated with estimated ASCVD risk among SA. Cardiometabolic risk factors are associated with CAC density and volume. Future longitudinal studies are required to demonstrate the interrelationship of advanced measures and cardiovascular risk factors with incident ASCVD outcomes.

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MASALA:

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Declaration of Competing Interest

Dr. Virani reports Research support: Department of Veterans Affairs, World Heart Federation, Tahir and Jooma Family

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Table 1.

Baseline characteristics of the study population stratified by sex

	Overall (n=1,155)	Men (n=602)	Women (n=553)	p-value
Age, years	56.8 (9.4)	57.6 (9.9)	55.9 (8.8)	0.002
Greater than bachelor's degree	645 (56%)	386 (64%)	259 (47%)	<0.001
Annual family income >$100k	721 (62%)	382 (63%)	339 (61%)	0.32
Total cholesterol, mg/dL	187 (38)	180 (38)	194 (36)	<0.001
HDL-C, mg/dL	50 (14)	45 (11)	56 (14)	<0.001
LDL-C, mg/dL	111 (32)	108 (33)	114 (32)	0.002
Statin use	335 (29%)	204 (34%)	131 (24%)	<0.001
Waist circumference, cm	93.6 (10.2)	96.5 (9.4)	90.4 (10.2)	<0.001
BMI, kg/m^2	26.0 (3.9)	25.8 (3.7)	26.3 (4.2)	0.02
Hypertension	506 (44%)	295 (49%)	211 (38%)	<0.001
Current cigarette smoking status	36 (3%)	30 (5%)	6 (1%)	<0.001
Diabetes	315 (27%)	187 (31%)	128 (23%)	<0.001
*HOMA-IR	2.49 (1.63−3.89)	2.78 (1.87−4.35)	2.19 (1.47−3.37)	<0.001
*Exercise, METs/min/week	983 (315−1,890)	1,084 (420−2,010)	840 (315−1,770)	0.01
Western diet	296 (33%)	184 (39%)	112 (27%)	<0.001
Family history of CAD	547 (47%)	265 (44%)	282 (51%)	0.02
Liver fat attenuation, HU	55 (11)	52 (10)	58 (11)	<0.001
*Lp(a), mg/dL	17 (9−33)	16 (9−31)	19 (11−35)	0.006
*ASCVD risk score, %	4.51 (1.59−11.40)	8.31 (3.60−17.14)	2.16 (0.95−4.87)	<0.001
*CAC density	3.10 (2.35−3.53)	3.11 (2.45−3.53)	3.00 (2.00−3.55)	0.42
*CAC volume	0 (0−49)	15 (0−129)	0 (0−0)	<0.001

Abbreviations: HDL-C (high-density lipoprotein cholesterol), LDL-C (low-density lipoprotein cholesterol), BMI (body mass index), HOMA-IR (homeostatic model assessment for insulin resistance), METs (metabolic equivalents of task), CAD (coronary artery disease), Lp(a) (lipoprotein a), ASCVD (atherosclerotic cardiovascular disease), CAC (coronary artery calcium)

*Refers to continuous variables that are skewed and presented as median (interquartile range). Normally continuous variables are presented as mean (stand deviation) and categorical variables are presented as number (percentage)

Table 2.

Multivariable-adjusted beta coefficients (95% confidence interval) for the association of the pooled cohort equations with coronary artery calcium volume and density

	CAC Density	CAC Volume
Overall		
Unadjusted	0.25 (0.15,0.34)	0.48 (0.44,0.53)
Adjusted	0.24 (0.12,0.35)	0.43 (0.38,0.48)
Sex-Stratified		
Men	0.21 (0.08,0.35)	0.42 (0.32,0.52)
Women	0.14 (−0.15,0.43)	0.34 (0.26,0.42)

Abbreviations: CAC (coronary artery calcium)

Model is adjusted for education, annual family income, birth country, number of years spent in U.S. Results for CAC volume are additionally adjusted for CAC density and results for CAC density are additionally adjusted for CAC volume

Sex stratified analyses are presented for the multivariable-adjusted model only

Table 3.

Multivariable-adjusted beta coefficients (95% confidence interval) for the association of cardiovascular risk factors and coronary artery calcium density and volume

	CAC Density	CAC Volume
Total cholesterol, mg/dL	0.001 (−0.001,0.003)	−0.001 (−0.003,0.003×10$^{-3)}$
HDL-C, mg/dL	**0.009 (0.001,0.016)**	−0.004 (−0.009,0.001)
Waist circumference, cm	**−0.014 (−0.023,−0.004)**	0.006 (−0.002,0.011)
BMI, kg/m^2	−0.021 (−0.044,0.003)	**0.016 (0.002,0.030)**
Hypertension	−0.12 (−0.30,0.07)	**0.15 (0.04,0.26)**
Cigarette smoking status		
Never	0.00 (ref)	0.00 (ref)
Former	0.01 (−0.22,0.24)	−0.11 (−0.25,0.03)
Current	−0.09 (−0.52,0.33)	0.13 (−0.12,0.39)
Statin use	−0.03 (−0.21,0.15)	**0.16 (0.06,0.27)**
Glycemic status		
Normoglycemia	0.00 (ref)	0.00 (ref)
Prediabetes	−0.08 (−0.30,0.15)	0.08 (−0.06,0.21)
Diabetes	0.001 (−0.220,0.222)	**0.19 (0.06,0.32)**
HOMA-IR	−0.11 (−0.24,0.01)	**0.12 (0.04,0.19)**
Exercise, METs/min/week	0.003 (−0.032,0.037)	−0.01 (−0.03,0.01)
Dietary pattern		
Western diet	0.00 (ref)	0.00 (ref)
Sweets and refined grain	−0.07 (−0.29,0.16)	0.01 (−0.12,0.15)
Fruits and vegetables	0.04 (−0.19,0.26)	−0.04 (−0.17,0.10)
Family history of CAD	−0.03 (−0.21,0.14)	0.101 (−0.004,0.207)
Liver fat attenuation, HU	−0.001 (−0.011,0.009)	−0.001 (−0.007,0.005)
Lp(a), mg/dL	−0.03 (−0.15,0.10)	0.05 (−0.02,0.13)

Abbreviations: HDL-C (high-density lipoprotein cholesterol), LDL-C (low-density lipoprotein cholesterol), BMI (body mass index), HOMA-IR (homeostatic model assessment for insulin resistance), METs (metabolic equivalents of task), CAD (coronary artery disease), Lp(a) (lipoprotein a), ASCVD (atherosclerotic cardiovascular disease), CAC (coronary artery calcium)

Model is adjusted for age, sex, race, education, annual family income, birth country, number of years spent in U.S. Results for CAC volume are additionally adjusted for CAC density and results for CAC density are additionally adjusted for CAC volume **BOLDED** items are significant