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Cardiovascular risk-enhancing factors and coronary artery calcium in South Asian American adults: The MASALA study

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ABSTRACT

Objectives: The 2018 and 2019 U.S. guidelines for the management of cholesterol and primary prevention of atherosclerotic cardiovascular disease (ASCVD) recommend consideration of cardiovascular risk-enhancing factors (REFs), including South Asian ancestry, to refine ASCVD risk estimation. However, the associations of REFs with atherosclerosis are unclear in South Asian American adults, who have a disproportionately elevated premature coronary heart disease risk. In the Mediators of Atherosclerosis in South Asians Living in America (MASALA) cohort, we investigated associations of individual REFs, or the number of REFs, with coronary artery calcium (CAC).

Methods: Using baseline and follow-up data from MASALA, we evaluated the association of REFs (family history of ASCVD, low-density lipoprotein cholesterol ≥160 mg/dL, triglycerides ≥175 mg/dL, lipoprotein(a) >50 mg/dL, high-sensitivity C-reactive protein [hsCRP] ≥2.0 mg/dL, ankle-brachial index <0.9, chronic kidney disease, metabolic syndrome), individually and combined, with baseline prevalent CAC, any CAC progression (including incident CAC and CAC progression), and annual CAC progression rates using multivariable logistic regression and generalized linear models.

Results: Among 866 adults, mean age was 55 [SD 9] years and 47% were female. There were no significant associations of REFs with baseline prevalent CAC or any CAC progression (incident CAC and CAC progression at Exam 2) after adjustment. Among the 56% of participants who had any CAC progression, having 3+ REFs was associated with a significantly higher annual CAC progression rate (adjusted rate ratio [aRR] 1.94, 95% CI 1.39–2.72) vs. having 0 REFs. The annual CAC progression rate was 20% higher per additional REF (aRR 1.20, 95% CI 1.09–1.32). Findings were similar after excluding statin users, and among those with low 10-year ASCVD risk (<5%).

Conclusions: Among South Asian American adults, we found no association of REFs with prevalent CAC at baseline or having any CAC progression. Among those with any CAC progression, a higher number of REFs was associated with higher annual CAC progression rates.

1. Introduction

The 2018 and 2019 United States guidelines for the management of cholesterol and primary prevention of atherosclerotic cardiovascular disease (ASCVD) recommend consideration of cardiovascular risk-enhancing factors (REFs) to refine and personalize risk assessment, particularly among adults at borderline to intermediate ASCVD risk (5% to <20%). These REFs include family history of premature ASCVD, chronic kidney disease (CKD), ankle-branchial index (ABI) <0.9, triglycerides ≥175 mg/dL, low-density lipoprotein cholesterol (LDL-C) 160–190 mg/dL, metabolic syndrome (MetS), chronic inflammatory diseases, high-sensitivity C-reactive protein (hsCRP) ≥2 mg/dL,

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Table 1
MASALA study participant characteristics at baseline, overall and stratified by number of risk-enhancing factors, 2010–2018.

	Overall $n = 866$	0 REF $n = 188$	1 REF $n = 273$	2 REF $n = 213$	3+ REFs $n = 192$	P-value
Demographic Characteristics						
Age	55.3 (9.2)	54.8 (9.8)	55.1 (9.2)	55.5 (9.0)	55.6 (9.0)	0.82
Female sex	405 (46.8%)	81 (43.1%)	122 (44.7%)	104 (48.8%)	98 (51.0%)	0.35
Annual family income ≥$75,000[a]	619 (71.5%)	145 (77.1%)	210 (79.9%)	132 (63.8%)	132 (68.8%)	<0.01
Education ≥ Bachelor's	759 (87.6%)	171 (91.0%)	248 (90.8%)	183 (85.9%)	157 (81.8%)	0.01
Cardiovascular Factors						
Hypertension	430 (49.7%)	64 (34.0%)	111 (40.7%)	123 (57.8%)	132 (68.8%)	<0.01
Diabetes	169 (19.5%)	20 (10.6%)	40 (14.7%)	41 (19.3%)	68 (35.4%)	<0.01
Total cholesterol	187 (36)	178 (30)	186 (32)	188 (37)	197 (42)	<0.01
Current/former smoker	147 (17.0%)	29 (15.4%)	46 (16.9%)	38 (17.8%)	34 (17.7%)	0.21
10-year ASCVD risk%	7.6 (9.1)	6.5 (9.1)	7.0 (8.1)	7.7 (9.4)	9.6 (9.9)	<0.01
Statin use	236 (27.3%)	44 (23.4%)	68 (25.0%)	60 (28.2%)	64 (33.3%)	0.12
Coronary Artery Calcium						
Prevalent CAC at Exam 1	361 (41.7%)	70 (37.2%)	109 (39.9%)	94 (44.1%)	88 (45.8%)	0.29
CAC progression from Exam 1 to Exam 2[b]	383 (56.2%)	73 (48.3%)	127 (57.0%)	93 (56.7%)	90 (62.5%)	0.10
Annual CAC progression rate (per year)[c]	22 (52)	15 (28)	22 (52)	20 (40)	34 (76)	<0.01

Data presented as mean (standard deviation), or frequency (percent).

[a] Percent accounts for missing income data;.

[b] CAC progression percentages are among the $n = 682$ participants who have both Exam 1 and Exam 2 CAC measurements, with Exam 1 CAC score ≥0 and Exam 2 CAC score higher than Exam 1 CAC score;.

[c] Annual CAC progression rate is the average annual progression of CAC from Exam 1 to Exam 2 in Agatston units, among the $n = 682$ participants who have both Exam 1 and Exam 2 CAC measurements. ASCVD: Atherosclerotic cardiovascular disease.

lipoprotein(a) (Lp(a)) ≥50 mg/dL, apolipoprotein $B \geq 130$ mg/dL, and for women, premature menopause and pregnancy-associated conditions (e.g., preeclampsia) that increase ASCVD risk [1,2]. Additionally, South Asian ethnicity was identified as a REF due to the disproportionately elevated risk for premature ASCVD in this population compared with other Asian American subgroups and non-Hispanic White individuals [1, 3-5].

The observed higher ASCVD risk among South Asian adults is not fully explained by traditional ASCVD risk factors [6], and guideline-recommended methods to quantify absolute ASCVD risk based on the Pooled Cohort Equations may underestimate ASCVD risk for people of South Asian ancestry [7]. The associations of the guideline-identified REFs, individually or in combination, with subclinical or clinical ASCVD have not been quantified in South Asian American adults. In parallel, optimal clinical implementation of REFs for ASCVD risk assessment remains unclear [8]. In this analysis of the Mediators of Atherosclerosis in South Asians Living in America (MASALA) cohort, we investigated whether individual or number of REFs are associated with prevalent coronary artery calcium (CAC) [9], any CAC progression [10], and annual CAC progression rates to inform the clinical interpretation and application of REFs for ASCVD risk assessment in the South Asian American population.

2. Methods

MASALA is a community-based prospective cohort of 906 SA men and women aged 40–84 years at baseline enrollment (Exam 1) from 2010 to 2013. In 2015–2018, 749 participants completed a follow-up exam (Exam 2). The MASALA study protocol was approved by the institutional review boards of University of California San Francisco, and Northwestern University. All participants provided written informed consent. This analysis was exempt from review as non-human subject research by the Medical College of Wisconsin institutional review board. Participants were excluded if they were missing a CAC score ($n = 7$), 10-year ASCVD risk score ($n = 4$), or data on any REF ($n = 25$). Our final Exam 1 sample included 866 participants, with 682 who had repeat CAC data at the follow-up Exam 2.

2.1. Covariates

Methods for collection of Exam 1 baseline measures including laboratory and questionnaire-based data and CAC scores in MASALA have previously been described [11]. Briefly, demographic variables included age, sex (female and male), annual family income (<$75,000 or ≥$75,000 per year), highest education achieved (< Bachelor's degree or ≥ Bachelor's degree). Traditional cardiovascular risk factors included hypertension (self-reported treatment for hypertension, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg), diabetes mellitus (defined by the use of glucose-lowering medications or fasting plasma glucose ≥ 126 mg/dL or a 2-hour post-challenge glucose ≥ 200 mg/dL), obesity (body mass index [BMI] ≥ 27.5 kg/m^2, consistent with BMI thresholds associated with increased cardiovascular risk in Asian individuals) [12], and smoking status (never or former/current). Ten-year ASCVD risk was calculated by applying the Pooled Cohort Equations for White adults, consistent with guideline recommendations. Statin use among participants was recorded.

2.2. Risk-enhancing factors

The cardiovascular REFs included were family history of ASCVD (MASALA participants were not asked about a family history of premature ASCVD, so we used any family history of coronary heart disease, myocardial infarction, or stroke), CKD (defined as estimated glomerular filtration rate [eGFR] < 59 mL/min/1.73 m^2), ankle-brachial index (ABI) <0.9, triglycerides ≥175 mg/dL, low-density lipoprotein cholesterol (LDL-C) ≥160 mg/dL, MetS (defined based on National Cholesterol Education Program Adult Treatment Panel III criteria[13] as ≥ 3 of the following: fasting glucose >126 mg/dL, HDL < 40 mg/dL [men] or < 50 mg/dL [women], triglycerides >150 mg/dL, waist circumference >40 inches [men] or >35 inches [women], blood pressure > 140/90 mmHg), hsCRP ≥ 2.0 mg/dL, and Lp(a) > 50 mg/dL [1,2]. History of chronic inflammatory diseases, apolipoprotein B level, and factors specific to women (premature menopause or pregnancy-associated conditions) were not accounted for due to data not being collected, or due to few participants with these REFs.

Table 2
Association of risk-enhancing factors and prevalent CAC at Exam 1 in the MASALA study.

	Model 1 Odds Ratio (95% CI)	Model 2 Odds Ratio (95% CI)	Model 3 Odds Ratio (95% CI)
Family history of ASCVD ($n = 395$)	1.36 (0.98 - 1.89)	1.23 (0.87 - 1.72)	1.20 (0.85 - 1.68)
LDL-C ≥ 160 mg/dL ($n = 55$)	0.93 (0.48 - 1.79)	1.43 (0.65 - 3.15)	1.21 (0.54 - 2.70)
Triglycerides ≥ 175 mg/dL ($n = 154$)	1.13 (0.75 - 1.71)	1.03 (0.66 - 1.61)	1.01 (0.65 - 1.57)
Lp(a) > 50 mg/dL ($n = 119$)	1.02 (0.64 - 1.62)	1.02 (0.63 - 1.65)	0.95 (0.59 - 1.55)
hsCRP ≥ 2.0 mg/dL ($n = 297$)	0.84 (0.59 - 1.20)	0.66 (0.45 - 0.97)	**0.68 (0.46 - 0.99)**
MetS ($n = 295$)	**2.35 (1.66 - 3.33)**	1.40 (0.93 - 2.10)	1.38 (0.92 - 2.08)
Number of REFs			
0 REF ($n = 188$)	*Ref*	*Ref*	*Ref*
1 REF ($n = 273$)	1.19 (0.74 - 1.89)	1.10 (0.68 - 1.78)	1.08 (0.66 - 1.75)
2 REF ($n = 213$)	1.52 (0.94 - 2.47)	1.20 (0.72 - 2.01)	1.18 (0.70 - 1.98)
3+ REFs ($n = 192$)	**1.77 (1.07 - 2.91)**	1.08 (0.62 - 1.89)	1.02 (0.58 - 1.79)
Per 1 additional REF	**1.21 (1.05 - 1.38)**	1.05 (0.90 - 1.22)	1.03 (0.88 - 1.20)
Low-risk adults (10-year ASCVD risk < 5%)[a]			
Number of REFs			
0 REF ($n = 126$)	*Ref*	*Ref*	*Ref*
1 REF ($n = 160$)	1.80 (0.95 - 3.43)	1.64 (0.84 - 3.20)	1.55 (0.79 - 3.04)
2 REFs ($n = 112$)	**2.41 (1.22 - 4.79)**	**2.06 (1.01 - 4.18)**	1.99 (0.97 - 4.06)
3+ REFs ($n = 88$)	1.97 (0.92 - 4.23)	1.27 (0.55 - 2.93)	1.11 (0.48 - 2.61)
Per 1 additional REF	1.28 (1.05 - 1.56)	1.15 (0.92 - 1.43)	1.12 (0.90 - 1.40)

Odds ratios (95% confidence intervals) represent odds of prevalent CAC at Exam 1 associated with presence of the REF or number of REFs.

[a] Limited to participants with a low (<5%) 10-year ASCVD risk as defined by the Pooled Cohort Equations. Model 1: adjusted for age, sex, education, income; Model 2: Model 1 + adjusted for ASCVD risk factors (hypertension, diabetes, obesity, smoking status, total cholesterol); Model 3: Model 2 + adjusted for baseline statin use. Bold indicates statistically significant with $p<0.05$. ASCVD: atherosclerotic cardiovascular disease, hsCRP: high-sensitivity C-reactive protein, LDL-C: low density lipoprotein cholesterol, Lp(a): lipoprotein(a), MetS: metabolic syndrome. The association of REFs with CAC as a continuous variable, ln(CAC+1), is shown in Supplemental Table 3. Analyses with ABI < 0.9 ($n = 9$) and CKD ($n = 13$) are provided in Supplemental Table 1. They are excluded here because reliable statistical comparisons are limited by sample size.

2.3. Coronary artery calcium

CAC as a dependent variable was evaluated in three ways: (1) prevalent CAC at Exam 1, defined as an Agatson CAC score > 0 versus a score of 0 at Exam 1; (2) any CAC progression, defined as a CAC score at Exam 2 greater than the CAC score at Exam 1 (which includes participants with incident CAC: CAC=0 at Exam 1 and CAC > 0 at Exam 2 and CAC progression: CAC > 0 at Exam 1 and CAC at Exam 2 > CAC at Exam 1), versus no CAC progression (no change or negative change in CAC from Exam 1 to Exam 2); and (3) annual CAC progression rate, which only included participants with any CAC progression and defined as the absolute difference in CAC score between Exam 1 and Exam 2, divided by the absolute difference in age between Exam 1 and Exam 2.

2.4. Statistical analysis

Descriptive statistics were used to summarize participants characteristics, overall and across categorized number of REFs (0, 1, 2, 3+ REFs). Characteristics across categorized number of REFs were compared using a Chi-square test or Fisher's exact test for categorical variables, and Student's *t*-test for continuous variables. Due to sample size limitations, analyses were not stratified by sex.

First, to evaluate the cross-sectional association of REFs with prevalent CAC at Exam 1, multivariable logistic regression models were used, first for each REFs separately, and second for number of REFs (categorized as 0, 1, 2, or 3+ REFs). Models were adjusted sequentially: first, for demographic variables (age, sex, highest education, income); second, additionally for traditional cardiovascular risk factors (hypertension, diabetes, total cholesterol, obesity, smoking status); and third, additionally for statin use. In a secondary analysis, regression models were calculated excluding participants who were on statin medications at any point in the study (Exam 1 and/or Exam 2). Finally, linear regression models were calculated using number of REFs (categorized as 0, 1, 2, or 3+ REFs) as predictors of CAC as a continuous variable (transformed as ln[CAC+1]) at Exam 1. Findings were reported as adjusted marginal differences.

Second, to evaluate the association of REFs with CAC progression, logistic regression models were used to evaluate any CAC progression as a binary outcome (CAC progression vs. no CAC progression). Third, among participants with CAC progression, generalized linear models with Gamma distribution and log link were used to identify the ratio of the annual CAC progression rate in individuals with the REF relative to the annual CAC progression rate without the REF (i.e., an adjusted annual CAC progression rate ratio [aRR]). An aRR identifies the mean annual change in CAC among participants with a REF (or categorized number of REFs) relative to the mean annual change in CAC among participants without the REF (or categorized number of REFs). The above analyses were conducted for each REF individually, categorized number of REFs (0, 1, 2, 3+ REFs), and per 1 additional REF. Multivariable models were adjusted following the same sequence as aforementioned, with a fourth model additionally adjusting for those with baseline CAC=0.

Secondary analyses repeated the above regression models 1) after excluding participants who were on statin medications and 2) among participants with low 10-year ASCVD risk (<5%). All analyses were performed using SAS version 9.4 (SAS Institute, Cary NC), with a two-sided p-value < 0.05 considered statistically significant.

3. Results

3.1. Demographic characteristics

Table 1 shows participant demographics characteristics, stratified by number of REFs. The overall average age was 55 (standard deviation 9) years, and 47% were women. No differences in age, proportion female, statin use, or smoking status, were observed across number of REFs. Participants with more REFs had a higher frequency of hypertension, diabetes, and obesity, higher mean total cholesterol values, and higher estimated 10-year ASCVD risk. Participants with more REFs had a lower frequency of having a Bachelor's degree or higher, and lower frequency

of annual income ≥$75,000. Frequency of prevalent CAC at Exam 1 was similar across categories of REF frequency. The frequency of CAC progression was highest among participants with 3+ REFs. Among those who had CAC progression, the mean annual CAC progression was 15 Agatston units per year among those with 0 REFs, 22 Agatston units per year among those with 1 REF, 20 Agatston units per year among those with 2 REFs, and 34 Agatston units per year among those with 3+ REFs.

No significant interaction was observed between individual or number of REFs and 10-year ASCVD risk categorized as low: <7.5%, high: ≥7.5% in association with CAC.

3.2. Risk-enhancing factors and prevalent CAC at exam 1

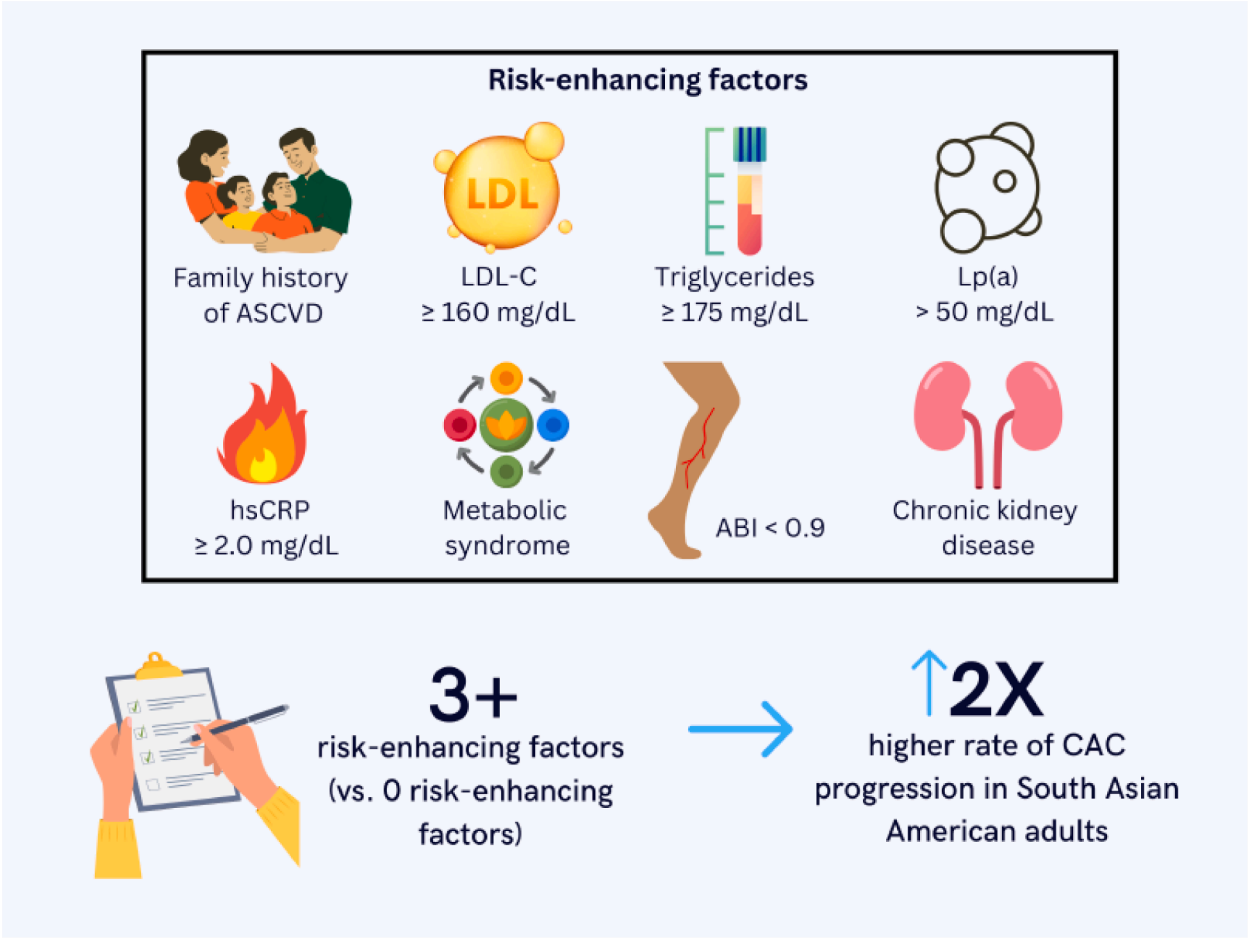
Table 2 shows the association of REFs with odds of prevalent CAC and CAC as a continuous variable at Exam 1. Data for ABI and CKD are listed in Supplemental Table 1 due to small sample size. In the model adjusted for demographic variables, prevalent CAC at Exam 1 was associated with metabolic syndrome (OR 2.35 [95% CI 1.66, 3.33]) and per 1 additional REF (OR 1.21 [95% CI 1.05, 1.38]). After adjusting for cardiovascular risk factors, these relationships were not significant (Supplemental Table 2). Similarly, number of REFs did not significantly predict CAC as a continuous variable (Supplemental Table 3).

3.3. Risk-enhancing factors and any CAC progression

Table 3 shows the odds of CAC progression from Exam 1 to Exam 2 associated with baseline REFs. Neither individual REFs nor number of REFs were significantly associated with a higher odds of CAC progression after adjustment for demographic factors, cardiovascular risk factors, statin use, and baseline CAC. Lp(a) ≥ 50 mg/dL (OR 1.91 [95% CI 1.12, 3.28]) was significantly associated with CAC progression after adjusting for cardiovascular factors but was not significant after adjusting for statin use. Findings were similar after excluding those on statin treatment (Supplemental Table 4).

3.4. Risk-enhancing factors and annual CAC progression rate

The association of baseline REFs with annual CAC progression rate among participants with any CAC progression is shown in Fig. 1 and Supplemental Table 5. Participants with a family history of ASCVD had a 31% higher annual CAC progression rate (adjusted rate ratio (aRR) 1.31 [95% CI 1.06, 1.63]) compared with those without a family history of ASCVD. However, after excluding those on statin treatment, the aRR was not significant (Supplemental Table 6). Participants with Lp(a) >50 mg/dL had a 75% higher annual CAC progression rate compared with those with Lp(a) ≤50 mg/dL (aRR 1.75 [95% CI 1.30, 2.35]), which remained significant after excluding those on statins. Participants with hsCRP ≥ 2.0 mg/dL had a 31% higher annual CAC progression rate compared with those with hsCRP <2.0 mg/dL (aRR 1.31 [95% CI 1.03, 1.67]), which remained significant after excluding those on statin treatment. Participants with 3 or more REFs had a 94% higher annual CAC progression rate compared to those with 0 REFs (aRR 1.94 [95% CI 1.39, 2.72]). Participants had a 20% higher annual CAC progression rate (aRR 1.20 [95% CI 1.09, 1.32]) for each additional REF present. These findings were similar after excluding participants using statins.



Central Illustration. Association of risk-enhancing factors with annual CAC progression in South Asian American adults. Eight risk-enhancing factors were evaluated in the association with coronary artery calcium, among South Asian American participants in the MASALA Study. Among participants with any CAC progression, having three or more of these risk-enhancing factors was associated with an approximately 2-times higher rate of CAC progression, compared with having no risk-enhancing factors.

Among participants with low (<5%) 10-year ASCVD risk, those with 3+ REFs had a higher annual CAC progression rate compared to those with 0 REFs (aRR 2.19 [95% CI 1.24, 3.87]). These low-risk participants had a 21% higher annual CAC progression rate (aRR 1.21 [95% CI 1.04, 1.41]) for each additional REF present.

Table 3
Association of risk-enhancing factors with any CAC progression in the MASALA study.

	Model 1 Odds Ratio (95% CI)	Model 2 Odds Ratio (95% CI)	Model 3 Odds Ratio (95% CI)	Model 4 Odds Ratio (95% CI)
Family history of ASCVD (n = 313)	**1.46 (1.01 - 2.11)**	1.30 (0.88 - 1.90)	1.23 (0.83 - 1.82)	1.25 (0.78 - 2.02)
LDL-C ≥ 160 mg/dL (n = 47)	1.07 (0.54 - 2.11)	1.05 (0.46 - 2.43)	0.85 (0.36 - 1.97)	0.63 (0.23 - 1.76)
Triglycerides ≥ 175 mg/dL (n = 119)	1.17 (0.73 - 1.87)	0.99 (0.60 - 1.62)	0.96 (0.58 - 1.59)	1.13 (0.63 - 2.01)
Lp(a) > 50 mg/dL (n = 92)	**1.91 (1.12 - 3.28)**	**1.83 (1.05 - 3.19)**	1.62 (0.92 - 2.83)	1.83 (0.96 - 3.50)
hsCRP ≥ 2.0 mg/dL (n = 225)	1.01 (0.68 - 1.49)	0.78 (0.52 - 1.19)	0.86 (0.56 - 1.31)	1.08 (0.65 - 1.81)
CKD (n = 8)	0.27 (0.05 - 1.57)	0.20 (0.04 - 1.07)	0.20 (0.03 - 1.12)	0.14 (0.01 - 1.57)
MetS (n = 215)	**2.01 (1.34 - 3.00)**	1.11 (0.69 - 1.81)	1.14 (0.70 - 1.87)	1.14 (0.62 - 2.09)
Number of REFs				
0 REF (n = 151)	*Ref*	*Ref*	*Ref*	*Ref*
1 REF (n = 223)	1.56 (0.94 - 2.59)	1.42 (0.84 - 2.40)	1.37 (0.80 - 2.32)	1.51 (0.78 - 2.95)
2 REFs (n = 164)	1.69 (0.98 - 2.90)	1.24 (0.70 - 2.18)	1.22 (0.68 - 2.17)	1.17 (0.56 - 2.42)
3+ REFs (n = 144)	**2.43 (1.38 - 4.26)**	1.42 (0.76 - 2.66)	1.31 (0.70 - 2.48)	1.83 (0.84 - 3.97)
Per 1 additional REF	**1.28 (1.10 - 1.50)**	1.09 (0.91 - 1.30)	1.07 (0.89 - 1.28)	1.15 (0.92 - 1.43)
Low-risk adults (10-year ASCVD risk < 5%)[a]				
Number of REFs				
0 REF (n = 100)	*Ref*	*Ref*	*Ref*	*Ref*
1 REF (n = 128)	1.42 (0.77 - 2.61)	1.36 (0.72 - 2.58)	1.21 (0.63 - 2.33)	1.13 (0.48 - 2.67)
2 REFs (n = 83)	1.53 (0.77 - 3.01)	1.23 (0.61 - 2.51)	1.20 (0.58 - 2.49)	0.89 (0.34 - 2.38)
3+ REFs (n = 69)	2.57 (1.26 - 5.24)	1.72 (0.78 - 3.79)	1.44 (0.64 - 3.25)	1.93 (0.71 - 5.24)
Per 1 additional REF	**1.34 (1.10 - 1.64)**	1.18 (0.94 - 1.47)	1.14 (0.91 - 1.44)	1.20 (0.89 - 1.61)

Odds ratios (95% confidence intervals) represent odds of any CAC progression (includes those with incident CAC and CAC progression at Exam 2) associated with presence of the REF or number of REFs.

[a] Limited to participants with a low (<5%) 10-year ASCVD risk as defined by the Pooled Cohort Equations. Model 1: adjusted for age, sex, education, income; Model 2: Model 1 + adjusted for ASCVD risk factors (hypertension, diabetes, obesity, smoking status, total cholesterol); Model 3: Model 2 + adjusted for baseline statin use; Model 4: Model 3 + adjusted for baseline prevalent CAC. Bold indicates statistically significant with $p<0.05$. ABI: ankle-brachial index, ASCVD: atherosclerotic cardiovascular disease, CKD: chronic kidney disease, hsCRP: high-sensitivity C-reactive protein, LDL-C: low density lipoprotein cholesterol, Lp(a): lipoprotein(a), MetS: metabolic syndrome. ABI not assessed individually due to small number of participants with ABI <0.9, this model was also limited by quasi separation, as all participants with ABI<0.9 had CAC progression.

4. Discussion

Among South Asian American adults in the MASALA Study, we found no independent association between individual REFs and prevalent CAC at Exam 1. We also found no independent association between individual REFs and having any CAC progression (incident CAC and CAC progression). Among those with any CAC progression, having Lp(a) > 50 mg/dL (compared to Lp(a) ≤ 50 mg/dL) and having hsCRP ≥ 2.0 mg/dL (compared to hsCRP < 2.0 mg/dL) was associated with a higher annual CAC progression rate. Among those with any CAC progression, including participants with low (<5%) 10-year ASCVD risk, having more REFs was associated with higher annual CAC progression rate (Central Illustration). These findings may inform the role of REFs in CAC progression among South Asian Americans, who were observed to have higher CAC progression compared to adults of other race and ethnic groups (particularly for men) [14]. These results may support consideration of REFs for further risk stratification, especially among South Asian American adults with low (<5%) 10-year ASCVD risk. However, assessment of the relationship between REFs and ASCVD outcomes, and optimal clinical implementation of REFs in ASCVD risk assessment, remain to be understood for South Asian individuals in the US.

Cardiovascular REFs, either individually or categorized by the number of REFs, have previously shown varying associations with CAC in other populations. In the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, family history of coronary heart disease was associated with a 55% higher odds for prevalent CAC after adjusting for cardiovascular risk factors and demographics [15]. While our findings demonstrate an association of family history of ASCVD with higher annual CAC progression rate, this finding was not significant after excluding those on statin treatment. This difference may in part have occurred due to limited follow-up in the MASALA cohort (one follow-up CAC exam, compared with four exams in MESA) which may have limited our ability to detect an association among those not on statin treatment. Further, there is known association of statin use and CAC progression, so our findings may in part reflect a higher of statins among individuals with a family history of ASCVD [16,17]. Inflammatory markers including hsCRP were positively associated with CAC progression in the MESA study[18]. In contrast to MESA findings, hsCRP was not independently associated with any CAC progression (includes incident CAC and CAC progression). Among those with any CAC progression, we observed a positive association between hsCRP and annual CAC progression rate, suggesting that hsCRP and the underlying inflammation may be related to progression of subclinical atherosclerosis among South Asian Americans.

Lp(a) was also associated with CAC in the MESA cohort [19]. While we observed that Lp(a) is not associated with CAC progression in the MASALA cohort (consistent with prior findings[14]) the observation that Lp(a) >50 mg/dL is associated with a higher annual CAC progression rate among those with any CAC progression suggests that Lp(a) may contribute to advancement of subclinical atherosclerosis in South Asian Americans. This observation may support measurement of Lp(a) as an independent marker of ASCVD risk among South Asian Americans, particularly those who have already developed CAC. Further research on the role of Lp(a) among South Asian Americans, including the underlying genetic variation that may contribute to disproportionate ASCVD risk among South Asian ancestry groups, will further contextualize our findings. Recent studies suggest that the magnitude of risk conferred by elevated Lp(a) may be different among individuals of different ancestry [20–23]. In the INTERHEART study sample, the risk of myocardial infarction attributable to high Lp(a) (>50 mg/dL) varied across ethnic groups, and was highest (9.5%) for South Asian individuals [24].

Importantly, while our data may be underpowered to detect associations between individual cardiovascular REFs with prevalent CAC or any CAC progression, we observed that a higher burden of REFs contributes to greater annual CAC progression rates, compared with those who have fewer REFs. Specifically, the observation that having 3+ REFs

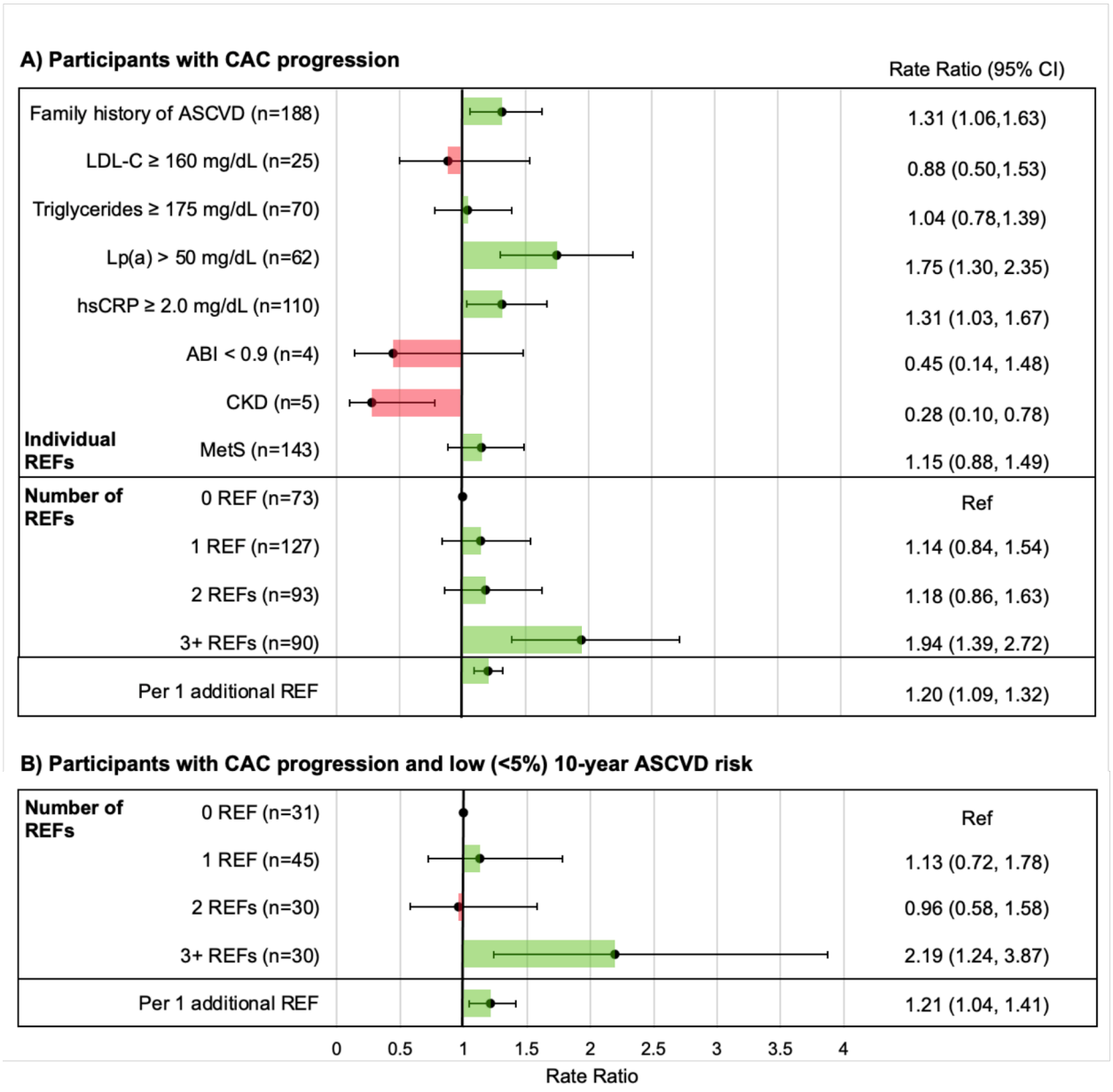


Fig. 1. Adjusted association of risk-enhancing factors with annual CAC progression among MASALA study participants with any CAC progression
Figure corresponds to fully adjusted model (Model 4) shown in Supplemental Table 5. Among participants with any CAC progression (includes those with incident CAC and CAC progression at Exam 2), adjusted annual CAC progression rate ratios (aRR) (95% confidence intervals) represent the ratio of annual CAC progression rates in participants with the REF (or number of REFs) relative to participants without the REF (or fewer REFs). For example, among participants with any CAC progression, after adjustment for all covariates, participants with a family history of ASCVD had a 31% higher CAC progression rate compared with participants without a family history of ASCVD. A: aRR by individual REFs (*reference: without REF*), number of REFs (*reference: 0 REFs)*, and per one additional REF *(reference: 1 less REF)*. B: Among those with low (<5%) 10-year ASCVD risk, aRR by number of REFs *(reference: 0 REFs)* and per one additional REF *(reference: 1 less REF)*. Adjusted for age, sex, education, income, ASCVD risk factors (hypertension, diabetes, obesity, smoking status, total cholesterol), baseline statin use, and baseline prevalent CAC. ABI: ankle-brachial index, ASCVD: atherosclerotic cardiovascular disease, CKD: chronic kidney disease, hsCRP: high-sensitivity C-reactive protein, LDL-C: low density lipoprotein cholesterol, Lp(a): lipoprotein(a), MetS: metabolic syndrome.

was associated with a higher annual CAC progression rate suggests that burden of REFs is important and a threshold effect of number of REFs may exist. These observations suggest that REFs may play an additive role in higher CAC progression rates among South Asian American adults. Given the limitations of current risk stratification tools for the South Asian population, these findings may support consideration of number of REFs in assessing ASCVD risk among South Asian American adults. In a recent study in the MESA cohort, the number of REFs provided less information for prediction of ASCVD events compared with CAC [25], but accounting for REFs may be a more accessible clinical assessment tool to inform cardiovascular risk among South Asian Americans in the setting of limited resources. Additionally, our findings suggest that REFs may help inform cardiovascular risk even among South Asian American adults with low (< 5%) calculated 10-year risk by the Pooled Cohort Equations. However, prospective data are needed to understand the relationship of REFs with ASCVD events and in risk stratification among South Asian Americans, as well as the optimal clinical implementation strategy to account for REFs among South Asian patients.

There are several limitations to consider. First, the baseline cross-sectional analyses limit causal inference. Second, due to sample size limitations and limited capture of female-specific REFs in ASCVD risk

assessment during MASALA Exam 1 data collection (2010–2013) which occurred prior to guideline publication, we report aggregated data adjusting for sex, rather than sex-stratified data. Accordingly, we did not include REFs specific to women, such as gestational diabetes or premature menopause. Future studies with larger samples of South Asian Americans would support stratification by sex. Third, it is acknowledged that guidelines recommended consideration of REFs in borderline- to intermediate-risk individuals to aid in risk stratification. Although our sample size did not facilitate stratification by ASCVD risk, our study found that among low-risk individuals with CAC progression, having more REFs was still associated with higher rates of annual CAC progression compared to adults with fewer REFs, suggesting that REFs may be informative even among those with low calculated risk. Fourth, the MASALA cohort has a small number of individuals with ABI<0.9 and CKD, which limited the power of individual analyses for these REFs. Nevertheless, South Asians generally have a lower prevalence of peripheral artery disease compared with other race and ethnic groups [26]. Additionally, South Asian adults living in South Asian countries have a worse CKD profile than those living in the US [27]. Accordingly, our analysis likely more closely reflects the South Asian American population from which our sample was derived. Fifth, ASCVD outcomes data are not yet available in the MASALA cohort. While CAC is highly predictive of ASCVD events, future analysis to evaluate the association of REFs with ASCVD events in this population is needed.

In conclusion, among South Asian American adults, there was no association of REFs with prevalent CAC or having any CAC progression (incident CAC and CAC progression). However, among those with any CAC progression, the number of REFs present was associated with higher annual CAC progression rates. Current guidelines that recommend consideration of REFs were largely based on data from White and Black populations, and prior to this analysis it was unclear whether REFs, or burden of REFs, were related to ASCVD risk among South Asian American adults. Although our findings are hypothesis-generating, they suggest that REFs may contribute to advancement of subclinical atherosclerosis among South Asian American adults. Specifically, considering overall REF burden, rather than individual REFs, may be useful in clinical ASCVD risk assessment and stratification among South Asian American adults. These data highlight the need to characterize the independent role of REFs in ASCVD outcomes and potential sex differences in associations to inform optimal clinical implementation of REFs in this high-risk population.

Disclosures

The authors report no disclosures.

Author contributions

HS and NSS designed the analysis for this study, HS and EG conducted the analysis, HS wrote the first draft, all authors provided critical revision of the manuscript and provided final review.

Declaration of Competing Interest

The authors report no conflicts of interest or disclosures.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2022.100453.

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