JACC: CARDIOVASCULAR IMAGING
VOL. 10, NO. 8, 2017

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2017.04.018

Coronary Artery Calcium Volume and Density

Potential Interactions and Overall Predictive Value: The Multi-Ethnic Study of Atherosclerosis

Michael H. Criqui, MD, MPH,[a] Jessica B. Knox, MD, MBA, MPH,[a] Julie O. Denenberg, MA,[a] Nketi I. Forbang, MD, MPH,[a] Robyn L. McClelland, PhD,[b] Thomas E. Novotny, MD, MPH,[c] Veit Sandfort, MD,[d] Jill Waalen, MD, MPH,[a] Michael J. Blaha, MD, MPH,[e] Matthew A. Allison, MD, MPH[a]

ABSTRACT

OBJECTIVES This study sought to determine the possibility of interactions between coronary artery calcium (CAC) volume or CAC density with each other, and with age, sex, ethnicity, the new atherosclerotic cardiovascular disease (ASCVD) risk score, diabetes status, and renal function by estimated glomerular filtration rate, and, using differing CAC scores, to determine the improvement over the ASCVD risk score in risk prediction and reclassification.

BACKGROUND In MESA (Multi-Ethnic Study of Atherosclerosis), CAC volume was positively and CAC density inversely associated with cardiovascular disease (CVD) events.

METHODS A total of 3,398 MESA participants free of clinical CVD but with prevalent CAC at baseline were followed for incident CVD events.

RESULTS During a median 11.0 years of follow-up, there were 390 CVD events, 264 of which were coronary heart disease (CHD). With each SD increase of *ln* CAC volume (1.62), risk of CHD increased 73% ($p < 0.001$) and risk of CVD increased 61% ($p < 0.001$). Conversely, each SD increase of CAC density (0.69) was associated with 28% lower risk of CHD ($p < 0.001$) and 25% lower risk of CVD ($p < 0.001$). CAC density was inversely associated with risk at all levels of CAC volume (i.e., no interaction was present). In multivariable Cox models, significant interactions were present for CAC volume with age and ASCVD risk score for both CHD and CVD, and CAC density with ASCVD risk score for CVD. Hazard ratios were generally stronger in the lower risk groups. Receiver-operating characteristic area under the curve and Net Reclassification Index analyses showed better prediction by CAC volume than by Agatston, and the addition of CAC density to CAC volume further significantly improved prediction.

CONCLUSIONS The inverse association between CAC density and incident CHD and CVD events is robust across strata of other CVD risk factors. Added to the ASCVD risk score, CAC volume and density provided the strongest prediction for CHD and CVD events, and the highest correct reclassification. (J Am Coll Cardiol Img 2017;10:845–54)

Cardiovascular disease (CVD), which includes coronary heart disease (CHD) and stroke, is a leading cause of morbidity and mortality in the United States and often remains undetected until it has resulted in clinical events (1). Coronary artery calcium (CAC) is a robust subclinical marker of atherosclerotic burden and is a strong predictor of CVD events (2–6).

From the [a]Department of Family Medicine and Public Health, University of California, San Diego, La Jolla, California; [b]Department of Biostatistics, University of Washington, Seattle, Washington; [c]Division of Epidemiology and Biostatistics, San Diego State University, San Diego, California; [d]National Institutes of Health Clinical Center, Department of Radiology and Imaging Sciences, Bethesda, Maryland; and the [e]Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, Maryland. Funding for this project comes from National Institutes of Health, National Heart, Lung, and Blood Institute (NHLBI) R01HL116395. The MESA study was supported by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162,

ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

AUC = area under the curve

CAC = coronary artery calcium

CHD = coronary heart disease

CI = confidence interval

CT = computed tomography

CVD = cardiovascular disease

eGFR = estimated glomerular filtration rate

HDL-C = high-density lipoprotein cholesterol

HR = hazard ratio

SBP = systolic blood pressure

The standard method of quantifying CAC from noncontrast cardiac-gated computed tomography (CT) scans is the Agatston score (7). The Agatston method, which up-weights the area of calcified plaque for greater calcium density, assumes that both the area and density of calcified plaques are positively related to CVD events. However, MESA (Multi-Ethnic Study of Atherosclerosis) recently showed that in a model containing both CAC volume and density, CAC density was inversely associated with incident CVD events (8). Analyses also suggested that CAC density had a stronger inverse association with CVD events at lower versus higher levels of volume, but the finding was not statistically significant.

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To test the effect of CAC density by CAC volume, and the consistency of the density association across strata of age, sex, ethnicity, atherosclerotic cardiovascular disease (ASCVD) risk score, diabetes status, and renal function, we used updated MESA events data that reflected a mean of 10.3 years (median 11.0 years) of follow-up, with 390 CVD events, a 47% increase. We hypothesized that CAC volume or CAC density might have differential associations with CHD and CVD across demographic and risk variable subgroups. We also evaluated whether CAC volume and density added predictive value to the new ASCVD risk score (9).

METHODS

STUDY PARTICIPANTS. MESA is a prospective cohort study of 6,814 men and women aged 45 to 84 years, who were free of clinical CVD at the time of study enrollment. Participants were recruited from 6 regions across the United States: Baltimore, Maryland; Chicago, Illinois; Los Angeles, California; New York, New York; St. Paul, Minnesota; and Winston-Salem, North Carolina. The institutional review board of each field center approved MESA and all participants provided written informed consent. Detailed methodology for MESA has been published previously (10). Only the participants with CAC scores >0 (n = 3,398 of 6,814; 49.9%) were analyzed because plaque density could only be calculated in participants with prevalent CAC (8).

RISK FACTOR ASSESSMENT. Conducted from 2000 to 2002, baseline examinations consisted of detailed questionnaires on participant demographics, medical history, medication usage, physical activity, and diet, as well as anthropometric and vital signs measurements, blood and urine sample collections, and noncontrast cardiac-gated CT scans. Standardized procedures were used to measure height, weight, and resting blood pressure. Measures of glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and estimated glomerular filtration rate (eGFR) were obtained from fasting blood samples. Diabetes was defined as a fasting blood glucose level >125 mg/dl or use of hypoglycemic medications. Impaired renal function was defined as an eGFR <60 ml/min/1.73 m^2. Smoking status was categorized as "yes" if the participant reported smoking cigarettes in the past 30 days. We calculated the ASCVD, a newly recommended scoring method developed from 5 pooled cohorts, which uses age, sex, total cholesterol, HDL-C, systolic blood pressure (SBP), use of antihypertensive medication, diabetes status, smoking status, and race/ethnicity to estimate a race-specific 10-year risk of CVD events (9).

CAC was measured by either electron-beam CT scanner (Chicago, Los Angeles, and New York) or a multidetector CT system (Baltimore, St. Paul, and Winston-Salem) (11). Electron-beam CT scanners produced image slices 3.0 mm thick, whereas multidetector CT systems produced image slices 2.5 mm thick. All scans were cardiac gated, phantom adjusted, and read centrally at the MESA CT reading center by 2 trained CT image analysts, yielding high-quality CAC measurements with high reproducibility and high comparability between scanner types (11–13).

Agatston and volume scores were provided in the original MESA dataset (12), and area and density scores were derived according to the methods described in a prior paper evaluating CAC density (8). Briefly, the Agatston score is calculated by multiplying the calcified plaque area of a given lesion within a given CT slice by a calcium density factor (1 to 4) that corresponds to the maximal Hounsfield unit attenuation. Scores for all lesions on all slices through the z-axis of the heart are summed to produce the

N01-HC-95163, N01-HC-95164, N01-HC-95165, and N01-HC-95169 from the NHLBI. All authors have reported that they have no relationships relevant to the contents of this paper to disclose. Dr. Novotny is now Deputy Assistant Secretary for Health in the U.S. Department of Health and Human Services. This work was completed during his previous position as a University of California San Diego/San Diego State University Faculty member. Drs. Criqui and Knox contributed equally to this work.

Manuscript received November 21, 2016; revised manuscript received March 30, 2017, accepted April 6, 2017.

TABLE 1 Demographic and Clinical Characteristics of Participants by Quartile of CAC Volume Score

	Volume Score, Quartile				
	1 (n = 852)	2 (n = 847)	3 (n = 850)	4 (n = 849)	All Participants (N = 3,398)
Volume range, mm^3	2.34–24.54	24.55–85.19	85.20–273.39	273.40–4,991.94	2.34–4,991.94
Age, yrs	62.45 ± 9.81	65.30 ± 9.32	67.44 ± 9.10	70.22 ± 8.10	66.35 ± 9.53
Male	420 (49.30)	454 (53.60)	511 (60.12)	579 (68.20)	1,964 (57.80)
Race/ethnicity					
Non-Hispanic white	340 (39.91)	320 (37.78)	391 (46.00)	446 (52.53)	1,497 (44.06)
African American	224 (26.29)	221 (26.09)	187 (22.00)	189 (22.26)	821 (24.16)
Hispanic	183 (21.48)	182 (21.49)	165 (19.41)	146 (17.20)	676 (19.89)
Chinese American	105 (12.32)	124 (14.64)	107 (12.59)	68 (8.01)	404 (11.89)
Smoking status	120 (14.13)	105 (12.43)	105 (12.35)	106 (12.51)	436 (12.86)
Systolic blood pressure, mm Hg	126.46 ± 20.59	130.55 ± 21.70	131.73 ± 21.61	134.51 ± 21.96	130.81 ± 21.65
Blood pressure treatment	308 (36.19)	363 (42.86)	409 (48.12)	472 (55.59)	1,552 (45.69)
Diabetes mellitus	113 (13.75)	129 (15.25)	158 (18.65)	203 (24.05)	607 (17.92)
Total cholesterol, mg/dl	196.95 ± 35.21	193.47 ± 36.94	194.81 ± 35.62	193.23 ± 37.96	194.62 ± 36.46
HDL-C, mg/dl	49.81 ± 13.90	49.73 ± 14.74	49.19 ± 14.77	48.92 ± 14.53	49.41 ± 14.49
eGFR	81.12 ± 17.53	78.81 ± 18.42	78.83 ± 24.19	77.08 ± 18.46	78.96 ± 19.87
Statin use	138 (16.22)	159 (18.77)	176 (20.71)	208 (24.50)	681 (20.05)
ASCVD score	0.13 ± 0.12	0.16 ± 0.13	0.20 ± 0.15	0.25 ± 0.15	0.19 ± 0.14
Density score	2.05 ± 0.74	2.70 ± 0.62	2.91 ± 0.47	3.11 ± 0.38	2.69 ± 0.69
Agatston score	9.55 ± 7.05	48.80 ± 21.47	170.92 ± 64.28	942.97 ± 802.04	292.92 ± 553.24
Agatston score	1–33	13–112	51–353	219–6,316	1–6,316
Hard CHD	34 (3.99)	46 (5.44)	82 (9.66)	102 (12.04)	264 (7.78)
Hard CVD	54 (6.34)	69 (8.16)	121 (14.25)	146 (17.24)	390 (11.49)

Values are range, mean ± SD, or n (%).

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CHD = coronary heart disease; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; HDL-C = high density lipoprotein cholesterol.

Agatston score. The area score was obtained by dividing the volume score in cubic millimeters by the appropriate slice thickness, either 2.5 mm or 3.0 mm depending on the scanner used. Finally, each participant's average density score was calculated by dividing the Agatston scores by their respective area scores.

CVD FOLLOW-UP. All participants were followed from baseline for incident CVD events (10,14). Telephone interviewers contacted each participant at 9- to 12-month intervals to collect information about interim hospitalizations, CVD outpatient diagnoses and procedures, and deaths. Medical records, death certificates, and next of kin interviews in the case of out-of-hospital deaths were used to verify self-reported diagnoses. Follow-up for this report started with baseline examination and concluded with the first CVD event, loss to follow-up, death, or December 31, 2012. Our outcome of interest was incident CVD events, which we analyzed as 2 separate endpoints: hard CHD, defined as myocardial infarction, resuscitated cardiac arrest, or CHD death; and hard CVD, defined as hard CHD, stroke, or stroke death. Each endpoint was adjudicated by the MESA Morbidity and Mortality Committee (14).

STATISTICAL ANALYSIS. We sorted the data to visualize the demographics, risk factors, and outcomes first by quartiles of volume, and then by quartiles of density. Because previous MESA analyses have shown a log linear relationship between CAC volume and CVD risk, we used the natural logarithm (*ln*) of the volume score in our analyses (5). After centering the *ln* volume and density variables, we conducted Cox proportional hazards regression to estimate the associations of *ln* volume and density with hard CHD and hard CVD events. Models were first adjusted for age, sex, race/ethnicity, total cholesterol, HDL-C, SBP, antihypertensive medication use, diabetes status, smoking status, and statin use. Models were alternatively adjusted for the ASCVD score, race/ethnicity, and statin use. We included the race/ethnicity term in the ASCVD models to capture any race effect that might be missed by the ASCVD score, which does not have parameters for Chinese and Hispanic individuals.

The adjusted models for both CHD and CVD were then stratified by the following variables: quartiles of CAC volume; age <65 versus >65; sex; 4 ethnic

TABLE 2 Demographic and Clinical Characteristics of Participants by Quartile of CAC Density Score

	Density Score, Quartile				
	1 (n = 849)	2 (n = 850)	3 (n = 849)	4 (n = 850)	All Participants (N = 3,398)
Density range	0.83–2.23	2.24–2.80	2.81–3.18	3.19–4.00	0.83–4.00
Age, yrs	62.80 ± 10.04	66.82 ± 9.47	67.69 ± 8.66	68.08 ± 9.00	66.35 ± 9.53
Male	441 (51.94)	498 (58.59)	511 (60.19)	514 (60.47)	1,964 (57.80)
Race/ethnicity					
Non-Hispanic white	373 (43.93)	407 (47.88)	437 (51.47)	280 (32.94)	1,497 (44.06)
African American	202 (23.79)	233 (27.41)	203 (23.91)	183 (21.53)	821 (24.16)
Hispanic	186 (21.91)	157 (18.47)	139 (16.37)	194 (22.82)	676 (19.89)
Chinese American	88 (10.37)	53 (6.24)	70 (8.24)	193 (22.71)	404 (11.89)
Smoking status	125 (14.74)	105 (12.38)	114 (13.48)	92 (10.84)	436 (12.86)
Systolic blood pressure, mm Hg	127.89 ± 21.30	131.44 ± 21.00	132.94 ± 21.42	130.98 ± 22.59	130.81 ± 21.65
Blood pressure treatment	340 (40.05)	399 (46.94)	415 (48.94)	398 (46.82)	1,552 (45.69)
Diabetes mellitus	137 (16.16)	163 (19.22)	151 (17.93)	156 (18.35)	607 (17.92)
Total cholesterol, mg/dl	195.54 ± 36.07	195.70 ± 36.87	193.91 ± 36.16	193.31 ± 22.59	194.62 ± 36.46
HDL-C, mg/dl	49.00 ± 13.91	49.11 ± 14.68	48.78 ± 14.29	50.76 ± 14.99	49.41 ± 14.49
eGFR	80.67 ± 18.44	79.43 ± 18.15	77.86 ± 24.27	77.89 ± 17.83	78.96 ± 19.87
Statin use	167 (19.69)	149 (17.53)	186 (22.01)	180 (21.18)	682 (20.10)
ASCVD score	0.14 ± 0.13	0.19 ± 0.14	0.21 ± 0.15	0.20 ± 0.15	0.19 ± 0.14
Volume score, mm^3	30.26 ± 46.78	183.83 ± 261.35	427.51 ± 602.14	389.78 ± 558.43	257.86 ± 460.36
Agatston score	22.32 ± 38.72	186.57 ± 279.45	499.11 ± 724.41	463.59 ± 681.69	292.92 ± 553.24
Agatston score	1–428	3–2,493	4–6,063	9–6,316	1–6,316
Hard CHD	49 (5.77)	74 (8.72)	81 (9.56)	60 (7.07)	264 (7.78)
Hard CVD	77 (9.07)	107 (12.60)	115 (13.58)	91 (10.72)	390 (11.49)

Values are range, mean ± SD, or n (%).
Abbreviations as in Table 1.

groups; ASCVD 10-year risk score <10%, 10% to 19%, and >20%; diabetes; and eGFR <60 versus >60. Each model was adjusted for the ASCVD risk score, except for the model stratified by the ASCVD risk score. Multiplicative interaction terms were tested for statistical significance.

We performed area under the curve (AUC) analyses to compare the predictive abilities of Model 1 = ASCVD score + race/ethnicity; Model 2 = Model 1 + *ln*(Agatston); Model 3 = Model 1 + *ln*(volume); and Model 4 = Model 1 + *ln* volume + density. Each of these models was analyzed for both CHD and CVD events. We also analyzed improvement in the continuous Net Reclassification Index for each model (15).

A 2-tailed alpha of <0.05 was considered statistically significant. All analyses were performed with SAS Studio version 3.2 and SAS 9.3 (SAS Institute Inc., Cary, North Carolina).

RESULTS

The participants were 58% male and had an average age of 66.4 years. Forty-four percent were white, 24% African American, 20% Hispanic, and 12% Chinese American persons. Four subjects were lost to follow-up and excluded from analysis. Table 1 shows that several demographic and clinical characteristics increased consistently across CAC volume quartiles, including age, SBP, eGFR, ASCVD, and CAC density scores, as well as the proportions of men, non-Hispanic white participants, treated blood pressure, statin use, and diabetes. There were a total of 390 CVD events, 264 of which were CHD events. Both incident CHD and CVD events increased across volume quartiles. Table 2 shows these characteristics by quartiles of density. The only consistent trend was an increase in age across quartiles.

Table 3 shows the results for Cox models fully adjusted for the individual CVD risk factors. The hazard ratios (HR) represent 1 SD of the independent variable. Adjusted for CAC density and the individual risk factors, the *ln* CAC volume score was a highly significant predictor of CHD and CVD with HRs of 1.73 (95% confidence interval [CI]: 1.45 to 2.05; $p < 0.001$) and 1.61 (95% CI: 1.39 to 1.85; $p < 0.001$), respectively. Adjusting the model for the ASCVD score, race/ethnicity, and statin use rather than the individual risk factors modestly strengthened the associations between *ln* CAC volume and CHD (HR: 1.83; 95% CI: 1.55 to 2.17; $p < 0.001$), and

TABLE 3 Multivariable HRs for *ln* Volume Score, Density Score, and Individual Risk Factors for Hard CHD and Hard CVD, All Variables in Both the CHD and CVD Models

	Hard CHD		Hard CVD	
	HR (95% CI)	p Value	HR (95% CI)	p Value
ln volume score, per SD	1.73 (1.45–2.05)	<0.001	1.61 (1.40–1.85)	<0.001
Density score, per SD	0.72 (0.60–0.86)	<0.001	0.75 (0.65–0.87)	<0.001
Age, yrs	1.04 (1.02–1.06)	<0.001	1.04 (1.03–1.05)	<0.001
Sex				
Female	1.00 [Reference]		1.00 [Reference]	
Male	1.36 (1.02–1.81)	0.037	1.20 (0.95–1.51)	0.132
Race/ethnicity				
Non-Hispanic white	1.00 [Reference]		1.00 [Reference]	
African American	1.07 (0.78–1.46)	0.686	1.02 (0.79–1.33)	0.880
Chinese	0.89 (0.56–1.43)	0.643	0.77 (0.51–1.16)	0.205
Hispanic	1.17 (0.84–1.62)	0.350	1.25 (0.96–1.63)	0.099
Total cholesterol, per SD	1.11 (0.98–1.25)	0.112	1.11 (1.00–1.23)	0.052
HDL-C, per SD	0.87 (0.75–1.01)	0.060	0.89 (0.79–1.00)	0.057
SBP, per SD	1.18 (1.04–1.33)	0.008	1.26 (1.14–1.39)	<0.001
Antihypertensive medication use				
No	1.00 [Reference]		1.00 [Reference]	
Yes	1.08 (0.83–1.41)	0.551	1.19 (0.96–1.48)	0.109
Diabetes				
No	1.00 [Reference]		1.00 [Reference]	
Yes	1.43 (1.07–1.91)	0.016	1.45 (1.14–1.85)	0.002
Current smoker				
No	1.00 [Reference]		1.00 [Reference]	
Yes	1.78 (1.27–2.50)	<0.001	1.80 (1.36–2.39)	<0.001
Statin use				
No	1.00 [Reference]		1.00 [Reference]	
Yes	1.01 (0.74–1.37)	0.964	0.87 (0.67–1.12)	0.279

ln volume SD = 1.62; CAC density SD = 0.69.
CI = confidence interval; HR, hazard ratio; SBP = systolic blood pressure; other abbreviations as in Table 1.

ln CAC volume and CVD (HR: 1.68; 95% CI: 1.46 to 1.92; $p < 0.001$).

Adjusted for CAC volume and the individual risk factors, each SD increase of CAC density was significantly associated with a 28% risk reduction for CHD (HR: 0.72; 95% CI: 0.60 to 0.86; $p < 0.001$) and a 25% risk reduction for CVD (HR: 0.75; 95% CI: 0.65 to 0.87; $p < 0.001$). After adjustment for the ASCVD score, race/ethnicity, and statin use, the CAC density score HR was essentially unchanged for both CHD (HR: 0.71; 95% CI: 0.60 to 0.85; $p < 0.001$) and CVD (HR: 0.75; 95% CI: 0.65 to 0.86; $p < 0.001$).

To test for the linearity of the multivariable inverse relationship of density with CHD and CVD, additional analyses looked at the HR for each quartile of density, with the first quartile as the reference (HR: 1.00). For CHD, the HRs for the second, third, and fourth quartiles of density were 0.77, 0.66, and 0.48, respectively. For CVD, the HRs were 0.74, 0.63, and 0.50, respectively. Thus, this inverse relationship was stepwise and linear, with the fourth quartile of density (≥3.19) associated with a halving of risk for CHD and CVD.

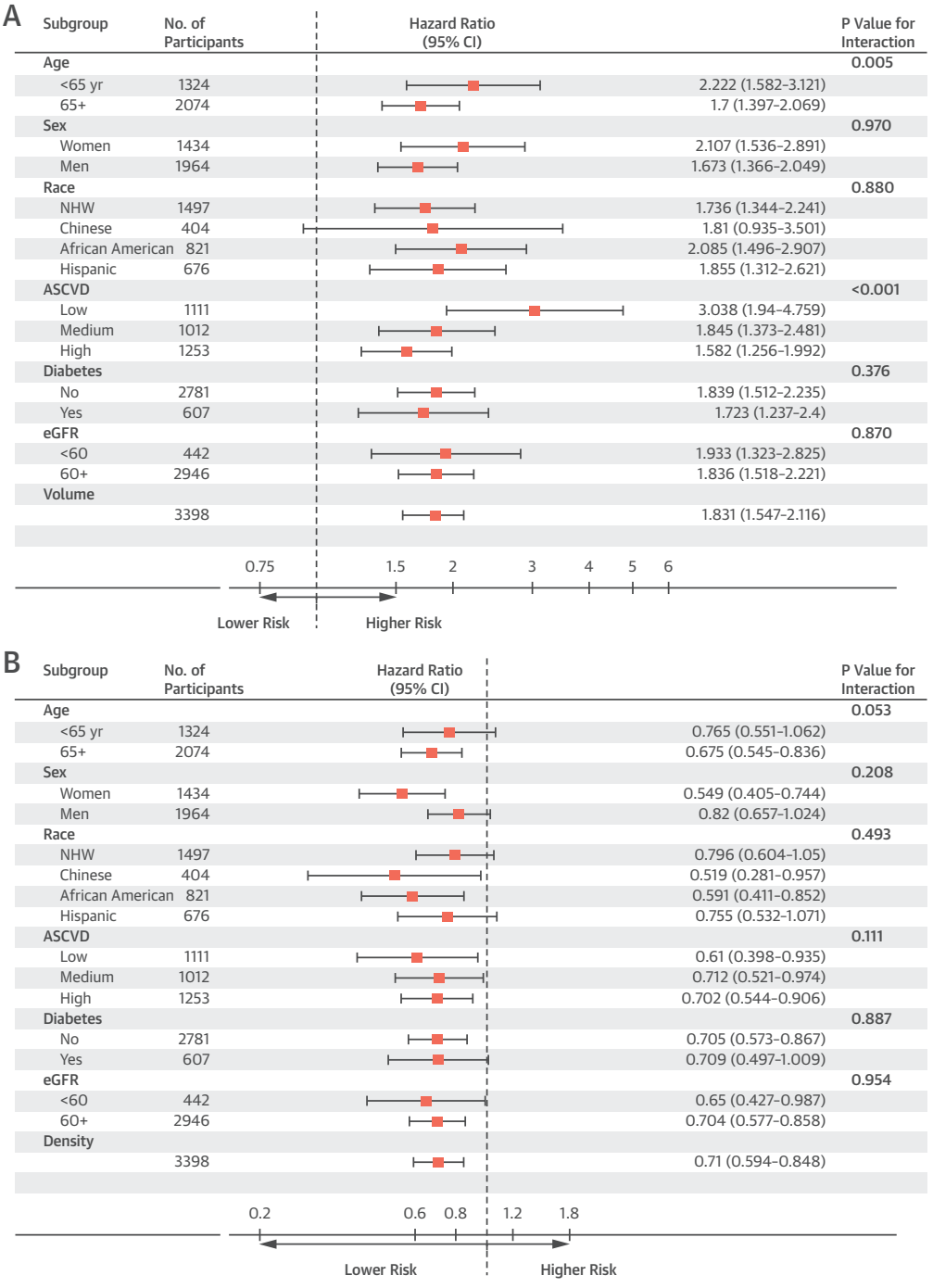
Table 4 displays the associations of CAC density with CHD and CVD, adjusted for *ln* CAC volume, the ASCVD risk score, race/ethnicity, and statin use and stratified by quartiles of volume. CAC density was consistently inversely associated with CHD and CVD

TABLE 4 Change in Hazard of Hard CHD and CVD Associated With a Change of 1 SD of CAC Density, Stratified by Quartile of CAC Volume, Adjusted for *ln* Volume, ASCVD, Race/Ethnicity, and Statin Use

	Hard CHD		Hard CVD	
Effect of Density at	HR	95% CI	HR	95% CI
Volume quartile 1	0.49	0.31–0.76	0.56	0.40–0.78
Volume quartile 2	0.64	0.45–0.92	0.79	0.60–1.04
Volume quartile 3	1.00	0.71–1.40	0.79	0.60–1.04
Volume quartile 4	0.67	0.45–0.99	0.77	0.56–1.06

CAC density SD = 0.69.
Abbreviations as in Tables 1 and 3.

FIGURE 1 Associations of CAC Volume and CAC Density With CHD and CVD Events, Stratified by Age, Sex, Race/Ethnicity, ASCVD Score, Diabetes, and eGFR



Hazard ratios are adjusted for the ASCVD risk score and race/ethnicity. The p value for the interaction term for each comparison is shown. **(A)** Stratified analyses of the CAC volume and CHD association. **(B)** Stratified analyses of the CAC density and CHD association. **(C)** Stratified analyses of the CAC volume and CVD association. **(D)** Stratified analyses of the CAC density and CVD association. ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CHD = coronary heart disease; CI = confidence interval; eGFR = estimated glomerular filtration rate; NHW = non-Hispanic white.

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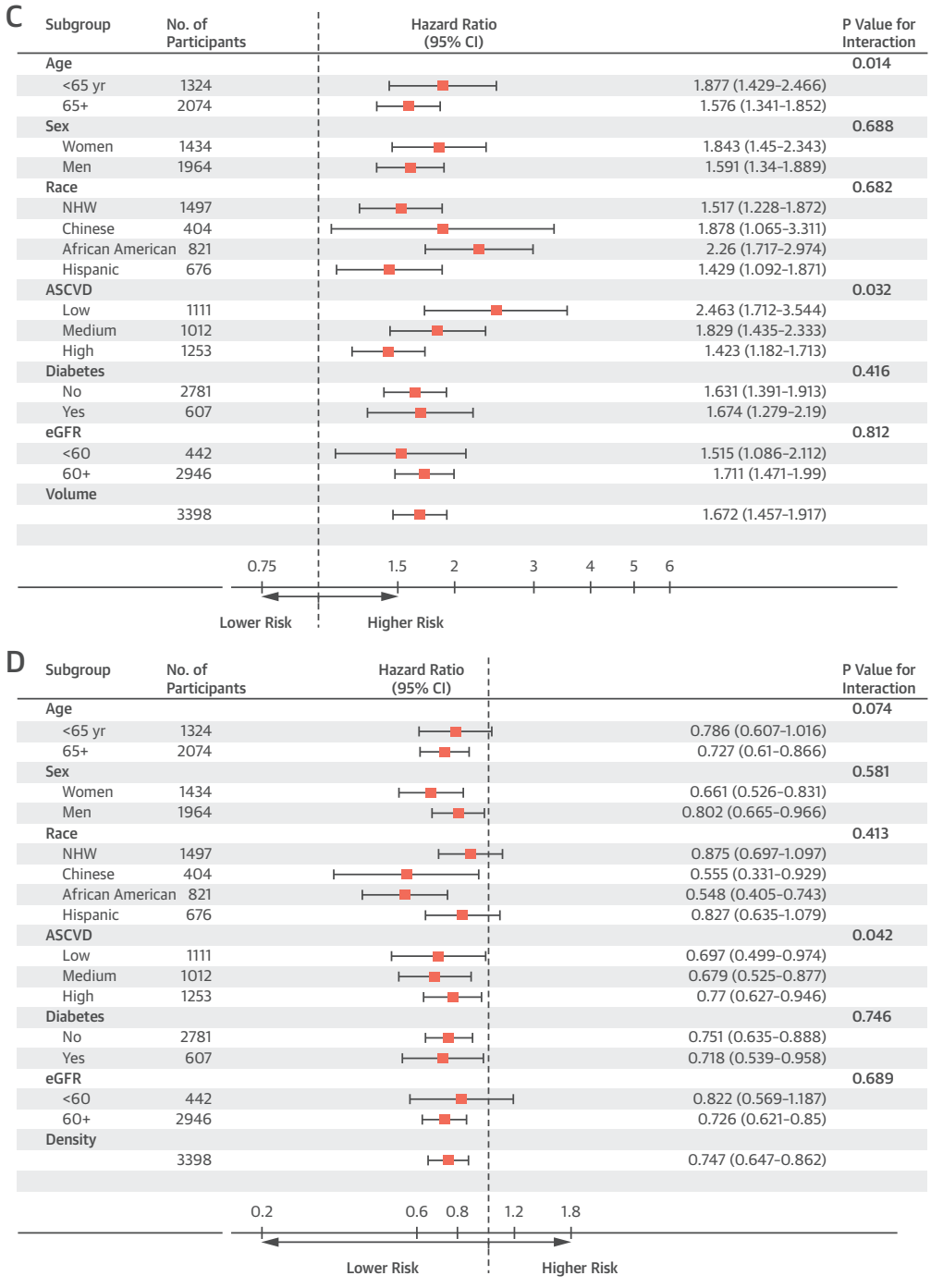
FIGURE 1 Continued



across levels of CAC volume, although the strongest inverse associations for density were in the first quartile of volume. Overall, there was no evidence for effect modification of the CAC density association by level of CAC volume. Similarly, in Cox models, the CAC volume × CAC density interaction terms were not significant for either CHD or CVD in the individual risks models ($p = 0.79$ and $p = 0.56$, respectively) or in the ASCVD models ($p = 0.77$ and $p = 0.50$, respectively) (data not shown).

TABLE 5 Areas Under the Receiver-Operating Curve for ASCVD Model and CAC Measures

Model #	Variables	CHD AUC	CHD p Value	CVD AUC	CVD p Value
1	ASCVD + race/ethnicity	0.653	–	0.664	–
2	Model 1 + *ln*(Agatston)	0.671	0.134 (vs. M1)	0.679	0.053 vs. M1
3	Model 1 + *ln*(volume)	0.675	0.061 (vs. M1)	0.683	0.022 vs. M1
4	Model 1 + *ln*(volume) + density	0.691	0.002 (vs. M1) 0.005 (vs. M2) 0.014 (vs. M3)	0.694	0.001 vs. M1 0.013 vs. M2 0.029 vs. M3

AUC = area under the curve; other abbreviations as in Table 1.

In Figure 1, HRs are adjusted for the ASCVD risk score and race/ethnicity. Figure 1A shows the separate CAC volume HR estimates for each of the subgroups for CHD. Each individual stratum HR was significant. The p values for the interaction terms are also shown. The lower risk groups had higher HRs. Significant interactions were present for age and ASCVD risk score. Figure 1B shows the separate CAC density HR estimates for each of the subgroups for CHD. Individual stratum HRs were significant or borderline. The lower risk groups had more strongly protective HRs, but none of the interactions were significant, although the results for age ($p = 0.07$) and ASCVD risk score ($p = 0.07$) were borderline. Figure 1C shows the separate CAC volume HR estimates for each of the subgroups for CVD. As for CHD, the interactions for age and the ASCVD risk score were significant, with the lower risk groups having the higher HR. Figure 1D shows the separate CAC density HR estimates for each of the subgroups for CVD. The interaction for ASCVD score was significant.

Table 5 displays the results of the AUC analyses. Model 1 contained the ASCVD score + race/ethnicity. Model 2 added *ln*(Agatston) to Model 1 and increased the AUC for CHD from 0.653 to 0.671 ($p = 0.134$) and the AUC for CVD from 0.664 to 0.679 ($p = 0.053$). Model 3 added *ln*(volume) to Model 1 and increased the AUC for CHD from 0.653 to 0.675 ($p = 0.061$) and the AUC for CVD from 0.664 to 0.683 ($p = 0.022$). Model 4 added *ln*(volume) and density to Model 1 and increased the AUC for CHD from 0.653 to 0.691 ($p = 0.002$) and the AUC for CVD from 0.664 to 0.694 ($p = 0.001$). Model 4 also significantly improved the AUC for both CHD and CVD when compared with either Model 2 or Model 3. The AUCs here are modestly lower than typically seen in CAC studies because a large amount of the predictive power for CAC is in the difference between no CAC and any CAC, whereas our study was of necessity limited to those with prevalent CAC.

In additional analyses we showed that a model containing only age, sex, ethnicity, and CAC volume and density showed a larger AUC (0.674) than Model 1 (AUC = 0.653), indicating CAC volume and density were more predictive than the combination of total cholesterol, HDL-C, SBP, hypertension medication use, diabetes, and current smoking.

Table 6 shows the results of the continuous Net Reclassification Index analyses, along with 95% CI. Compared with Model 1, Model 2, which added the Agatston score, improved classification by 25% for both CHD and CVD. Model 3, with the volume score, showed better reclassification, 31% for CHD and 27% for CVD. The highest reclassification was with both volume and density, with an improvement of 35% for both CHD and CVD.

TABLE 6 Continuous NRI for Multivariable Cox Proportional Hazard Models Comparison

	NRI Type	CHD Continuous NRI	CHD 95% CI (Bootstrapped)	CVD Continuous NRI	CVD 95% CI (Bootstrapped)
Model 2 vs. Model 1	Event	0.167	0.088–0.261	0.175	0.101–0.242
	Nonevent	0.085	0.039–0.150	0.079	0.032–0.123
	Total	0.252	0.143–0.016	0.254	0.149–0.353
Model 3 vs. Model 1	Event	0.174	0.087–0.256	0.165	0.081–0.227
	Nonevent	0.131	0.071–0.188	0.107	0.068–0.161
	Total	0.305	0.176–0.425	0.272	0.159–0.373
Model 4 vs. Model 1	Event	0.174	0.077–0.271	0.186	0.094–0.259
	Nonevent	0.172	0.111–0.228	0.160	0.103–0.206
	Total	0.347	0.216–0.468	0.345	0.225–0.442

NRI = Net Reclassification Index; other abbreviations as in Tables 1 and 3.

DISCUSSION

Consistent with prior observations (8), these data show that CAC density is inversely associated with CHD and CVD, whereas CAC volume is a positive predictor of both outcomes. There was little change in the inverse association between CAC density and CVD events with 3.4 years of additional follow-up. Whereas the prior analyses found CAC density HRs of 0.73 for CHD and 0.71 for CVD with each SD increase of CAC density when adjusted for the General Framingham Risk Score and race/ethnicity, we found CAC density HRs of 0.71 and 0.75 with each SD increase of CAC density when fully adjusted for the newly recommended ASCVD score, race/ethnicity, and statin use. Similarly, the prior analyses showed CAC volume HRs of 1.81 and 1.68 for CHD and CVD, respectively, and there was little change in these new data with CAC volume HRs of 1.83 and 1.68.

We found no interaction between CAC density and CAC volume for incident CHD or CVD events. The

inverse association between CAC density and incident CHD and CVD events seems to be consistent across levels of CAC volume such that all individuals with CAC would have lower risk for cardiovascular events with denser plaques regardless of the CAC volume burden. For CAC volume, interactions were shown for CHD and CVD for age and strata of the ASCVD score, where the lower risk groups showed the higher HR. The CAC density score showed significant interactions only for ASCVD strata predicting CVD. Although HRs tended to be modestly stronger for both CAC volume and density in lower risk groups, the absolute risks were higher in the higher risk groups because the baseline risk was higher (data not shown).

Table 5 shows that the volume score alone is superior to the Agatston score in improving risk prediction. The best prediction was with both CAC volume and density in the model. The predictive strength of the combination of CAC density with volume is illustrated by stronger AUC for these variables alone than for the risk factors included in the ASCVD risk score. Importantly, density can be derived from the same noncontrast cardiac CT scan protocol as the traditional Agatston score, so this information is immediately available. With the increasing evidence that CAC testing can be used to refine treatment decisions driven by an initial calculation of the ASCVD risk score (16), additional studies are needed to identify situations where density scores might further refine personalized decision-making. The current guidelines presently assign CAC testing a IIb recommendation when the decision to treat with a statin is unclear. Recent analyses from MESA have suggested that CAC testing is cost-effective in intermediate-risk patients, which some have interpreted as a 10-year ASCVD risk of 5% to 15% (17). Future research should compare the cost-effectiveness of CAC measurement augmented with density scores versus the ASCVD risk estimator for CVD risk stratification.

STUDY LIMITATIONS. An important limitation of our study is the limited range of CAC density, which we categorized by the arbitrary 4-point scale used in the Agatston score. Measured in Hounsfield units (HU), CAC density is a continuous measure ranging from 130 to >3,000 HU. The highest score (4) on the 4-point scale used here represented all CAC densities of 400 HU or greater. Use of such a crude scale may have collapsed some of the differential effect of very high densities on CHD and CVD risk, and our data may underestimate the density effect at high levels. Additionally, the density score used here is only the average density for each participant, and range of density scores may also be important to consider. Another limitation is that traditional CAC scoring does not account for the location (proximal vs. distal, focal vs. diffuse) or dispersion of the density, which may also affect the risk for cardiovascular events (18–20).

CONCLUSIONS

The inverse association of CAC density with incident CHD and CVD events is consistent across all levels of CAC volume, and across multiple strata of other risk variables. Future research should focus on integrating density into CAC scoring and identifying clinical situations where such advanced risk stratification might be most useful.

ACKNOWLEDGMENTS The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions.

ADDRESS FOR CORRESPONDENCE: Dr. Michael H. Criqui, Department of Family Medicine and Public Health, University of California San Diego, 9500 Gilman Drive #0607, La Jolla, California 92093-0607. E-mail: mcriqui@ucsd.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CAC measured by computed tomography has been shown to significantly improve risk prediction for CVD events beyond standard risk scores based on combinations of CVD risk factors. The Agatston has been by far the most widely used CAC score. The Agatston score is upweighted for denser CAC. However, recent research has shown that increased CAC density is actually associated with lower CVD risk at any given level of CAC volume. This paper demonstrates that the effect of CAC density was consistent at any level of CAC volume, and consistent across age, sex, and ethnicity, and levels of standard CVD risk factors. In addition, the CAC volume score significantly improved prediction compared with the Agatston score, and the addition of CAC density to CAC volume further significantly improved the prediction of CVD events. This suggests that measurement of CAC volume and CAC density provides improved CVD risk prediction.

TRANSLATIONAL OUTLOOK: Further research should address whether other CAC characteristics, such as specific arteries affected, and the distribution of CAC along the arteries, could further improve CVD prediction. Finally, further research should also delineate where such advanced risk stratification could provide clinical benefit.

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KEY WORDS cardiovascular diseases, coronary artery calcium, epidemiology